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THE A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN is published by the American Medical Association as a medium for the advancement of knowledge of the diseases of children and for the publication of scientific investigation in this field.

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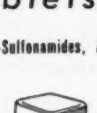

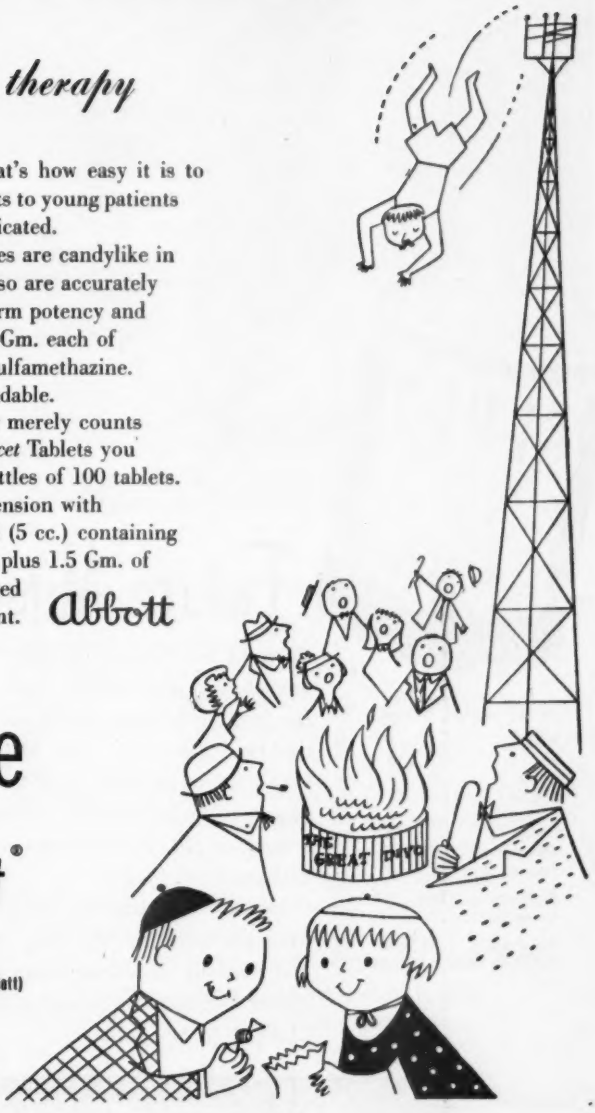

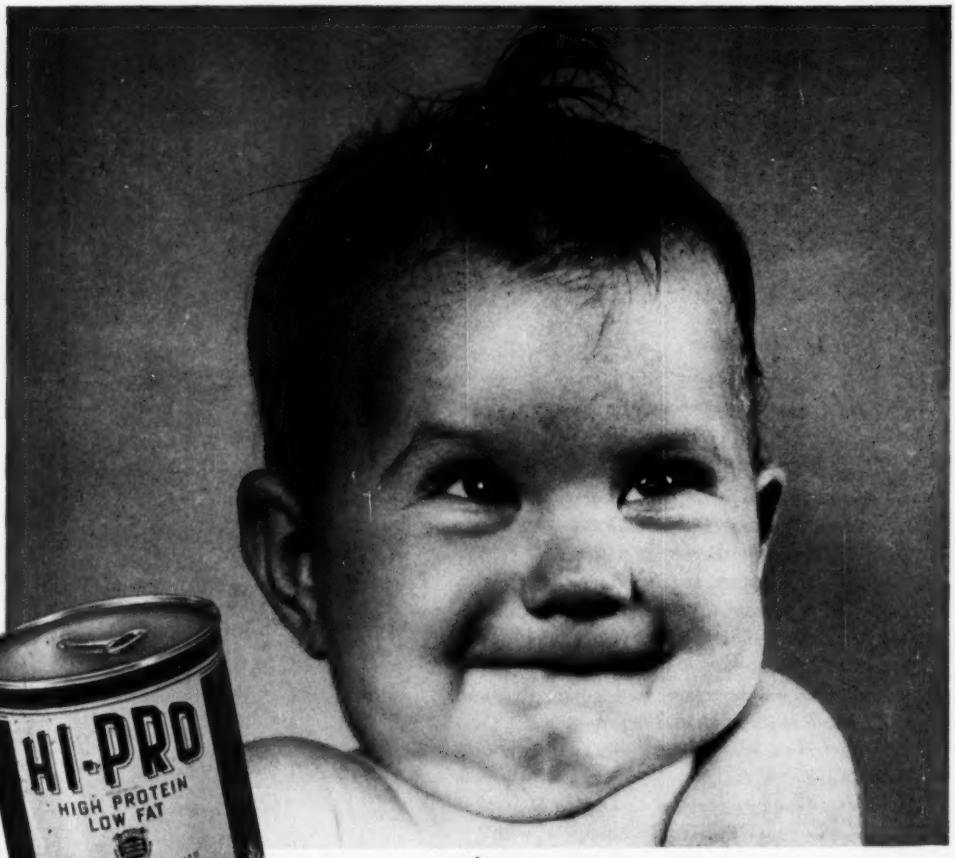

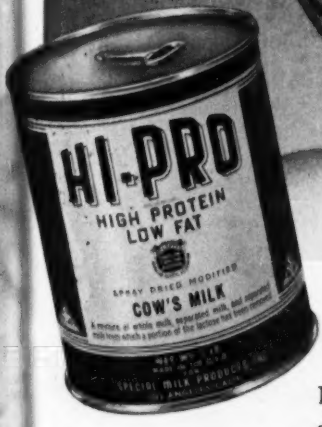

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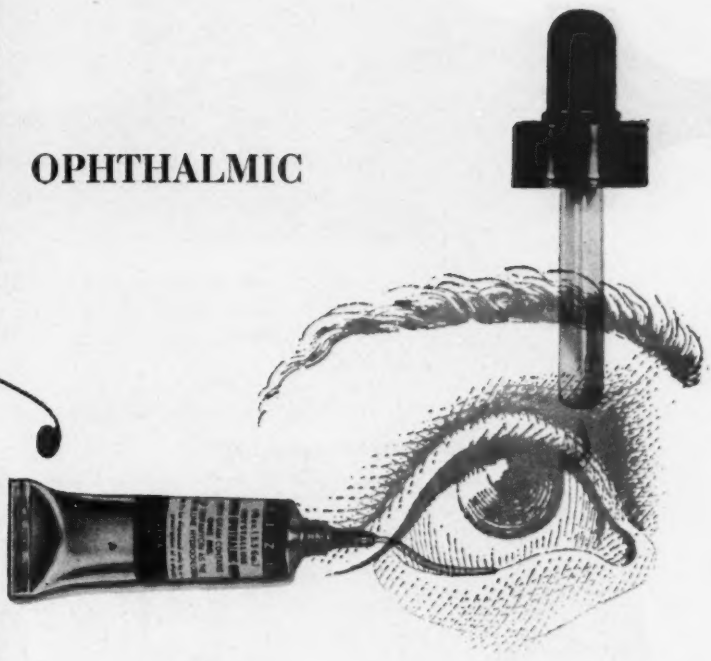

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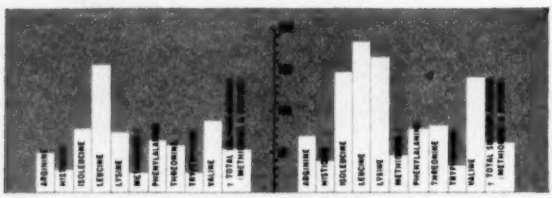

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1. *National Research Council: The Composition of Milks, Bull. 119, 1950.*
2. *Salmi, T.: Acta Paediatrica 31:1, 1944.*
3. *Spiess: Monatschr. f. Kinderhk. 97:242, 1949.*

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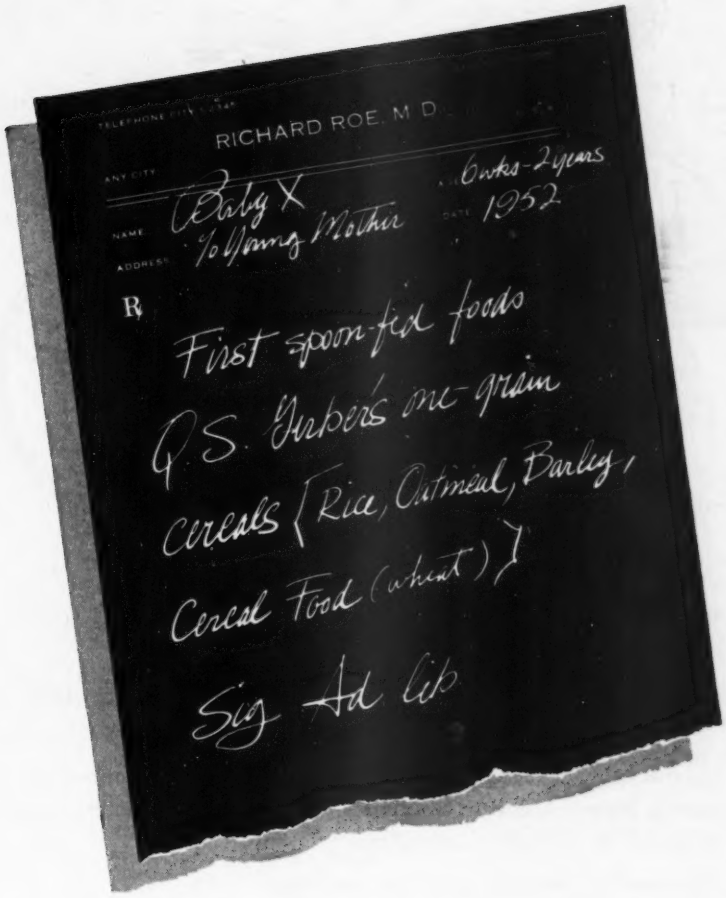

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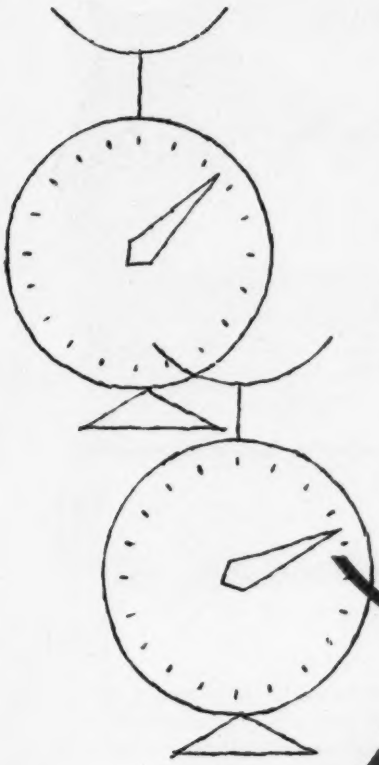

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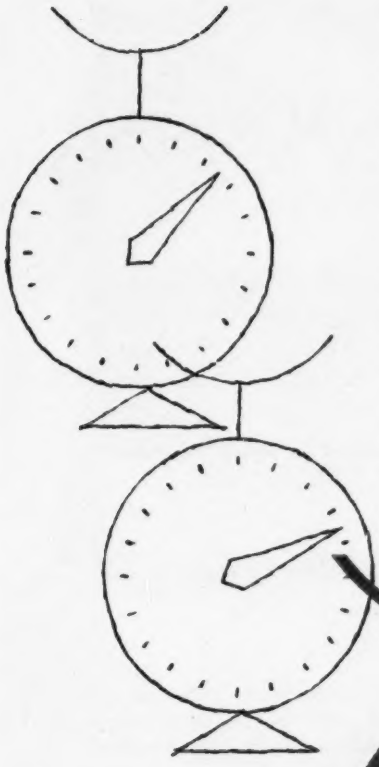

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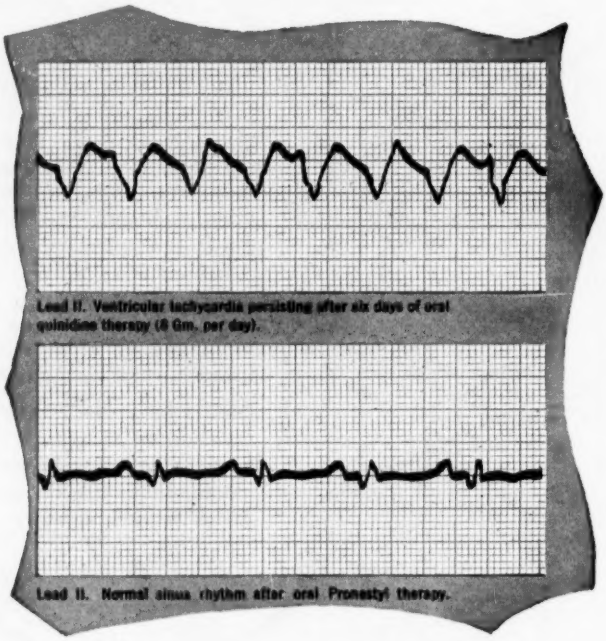

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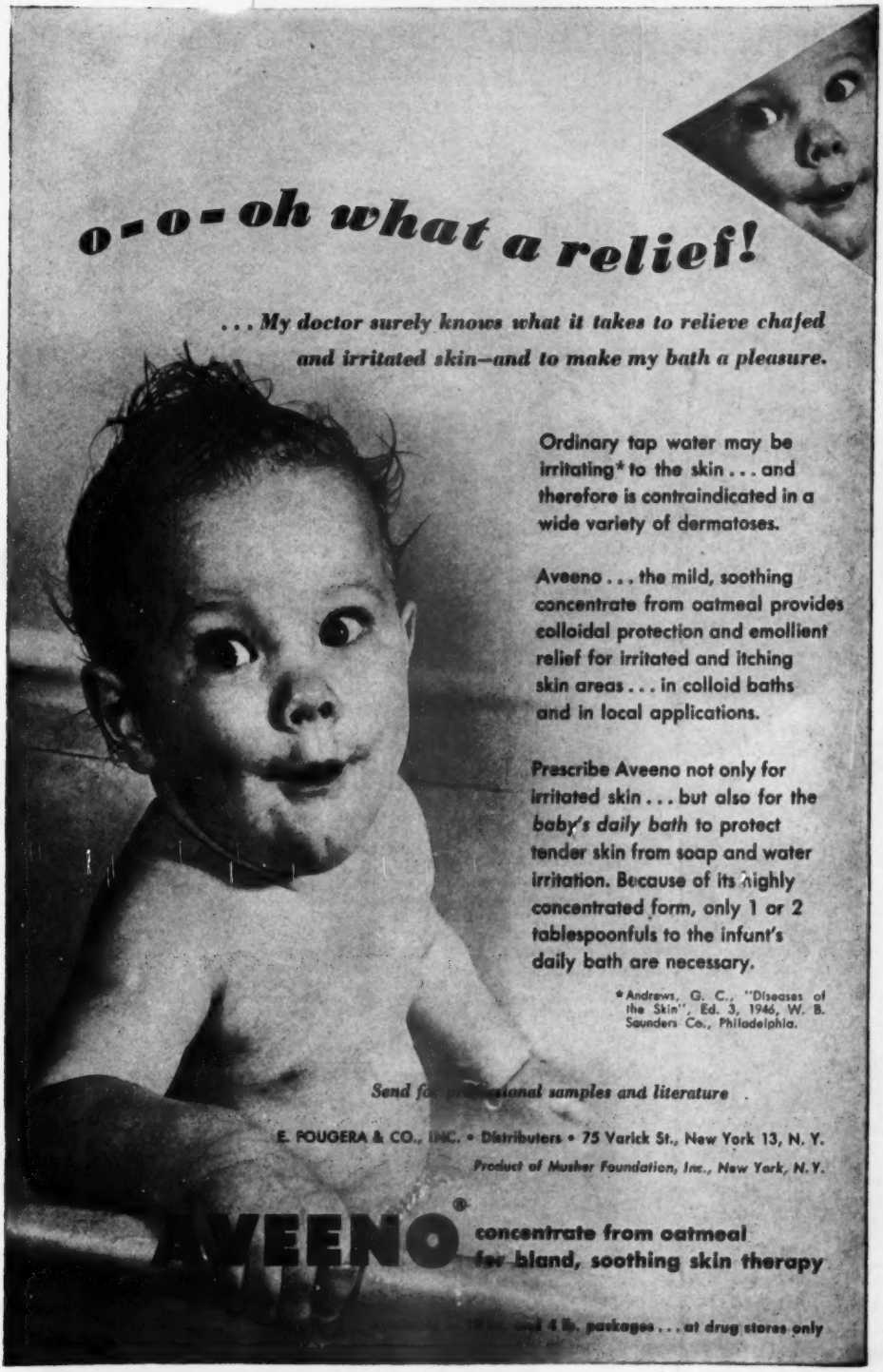
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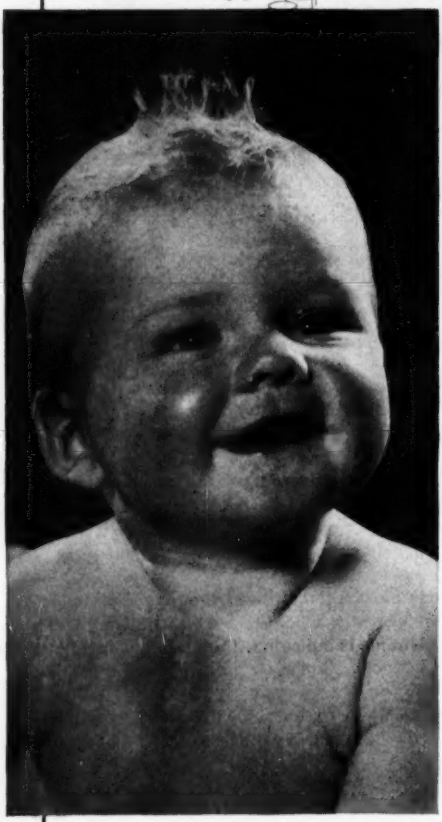

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STUDIES ON INTERSTITIAL GIANT CELL PNEUMONIA

I. Report of Five Cases with Autopsy

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INTERSTITIAL pneumonia may appear in different morphological forms and may be caused by various agents. Besides the interstitial pneumonia found in various known viral, rickettsial, fungal, and protozoal diseases,[1] and besides the syphilitic pneumonia alba, there are certain forms of unknown origin which may be differentiated on morphological or clinical grounds. This group includes the following conditions:

(*a*) The condition described by Hamman and Rich[2] as acute diffuse interstitial fibrosis, characterized clinically by acute symptoms and histologically by fibroblastic invasion of the alveolar walls.

(*b*) The disease entity called eosinophilic pneumonia (Loeffler), characterized by focal infiltrations of the interstitial tissue with eosinophilic cells.

(*c*) The so-called acute interstitial pneumonitis or atypical pneumonia, which occurs mainly in adults.[3]

(*d*) A group of diseases, including the so-called plasma cell pneumonia, the virus pneumonia of infants, and the *interstitielle Pneumonie der Frühgeburten,* which are possibly identical and which occur mainly in infants.[4] In this group inclusion bodies were often found in the alveolar

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2. Hamman, L., and Rich, A. R.: Acute Diffuse Interstitial Fibrosis of the Lungs, Bull. Johns Hopkins Hosp. **74**:177, 1944, cited by Gunn, F. D., in Synopsis of Pathology, edited by W. A. D. Anderson, Ed. 2, London, Henry Kimpton, 1946.

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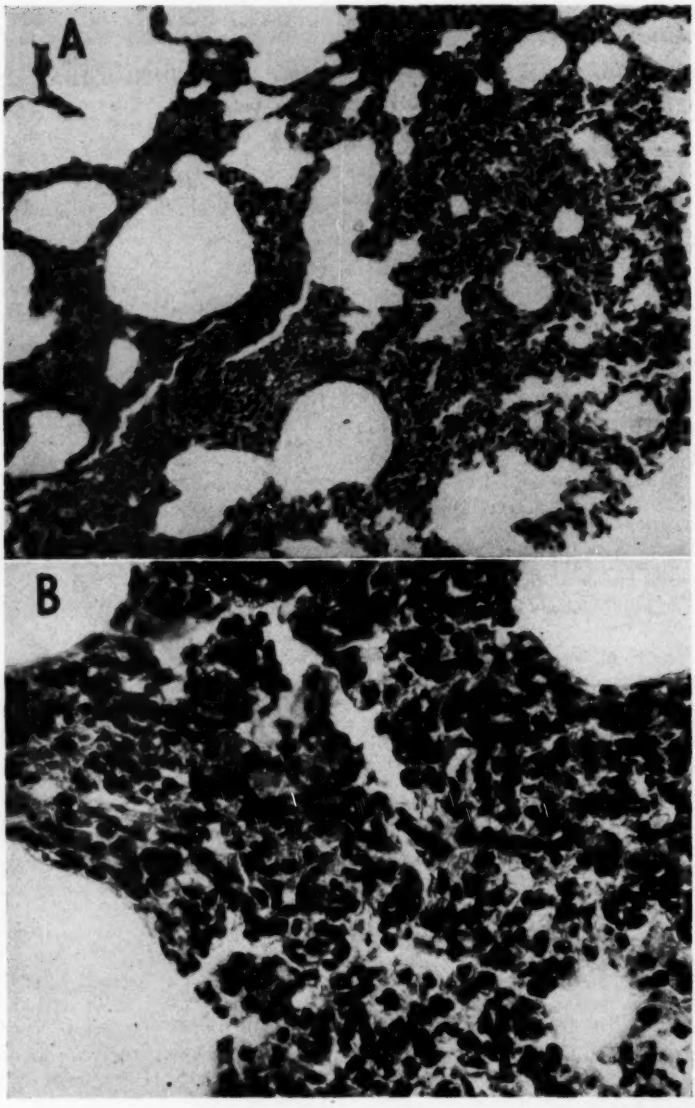

Fig. 1 (Case 1).—*A*, patch of interstitial infiltration bordering on an area of emphysema; × 115. *B*, thickened alveolar septum infiltrated with histiocytes, mononuclear cells, and a few polymorphonuclear leucocytes; × 470.

and bronchial lining cells, and viral origin has been suggested by most authors. The disease was found to occur mainly in premature infants, in most instances within three months after birth. Freudenberg and Tobler suggested that the appearance of the disease at this age might be explained by the decrease in the titer of maternal antibodies in the infants' blood.

(*e*) Giant cell pneumonia, characterized by the presence of multinucleated giant cells lining the walls of alveoli and bronchi, besides the common features of interstitial pneumonias.

This paper deals with the clinical and pathological findings in five cases of interstitial giant cell pneumonia in which autopsies were done and which occurred between December, 1949, and June, 1950. Two cases were found and the autopsies done in Jerusalem (Cases 4 and 5), while the other three occurred in the Rosh Haayin Hadassah Children's Hospital (Cases 1, 2 and 3). The Rosh Haayin cases were found in a consecutive series of 25 autopsies. The series contained nine other cases of interstitial pneumonia without giant cells.

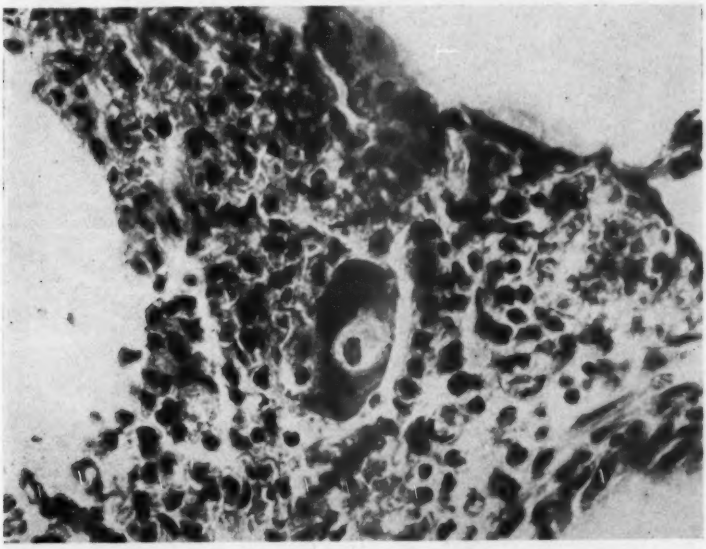

Fig. 2 (Case 2).—An alveolar lumen lined on one side by cuboidal epithelium, containing a large giant cell; × 530.

REPORT OF CASES

Case 1.—A 2-month-old girl was admitted on May 5, 1950, to the hospital because of diarrhea and malnutrition. The clinical examination on admission revealed persistent coughing and the presence of scattered sonorous rhonchi in the chest, with no evidence of consolidation.

During the 14 days of hospitalization, the following symptoms developed gradually. On May 12 the pharynx became swollen and congested and remained so for the duration of the disease. On May 15, a few rales were heard over the base of each lung. Six days later crepitations could be heard all over the chest. The crepitations persisted with diminished intensity during hospitalization. On May 29 the patient died.

During the patient's stay in the hospital the temperature was either normal or subfebrile, except for a rise to 103.3 F. after a blood transfusion.

The reaction to the Mantoux test, 1 : 10,000, was negative. A stool culture was also negative. The leucocytes numbered 13,000 per cubic millimeter, and no differential count was made.

Treatment consisted of penicillin, 150,000 units daily; streptomycin, 1 gm. daily; sulfadiazine, 1 gm. daily; vitamin A, vitamin B complex, and calciferol in high doses, and a transfusion of 70 cc. of blood and isotonic sodium chloride solution.

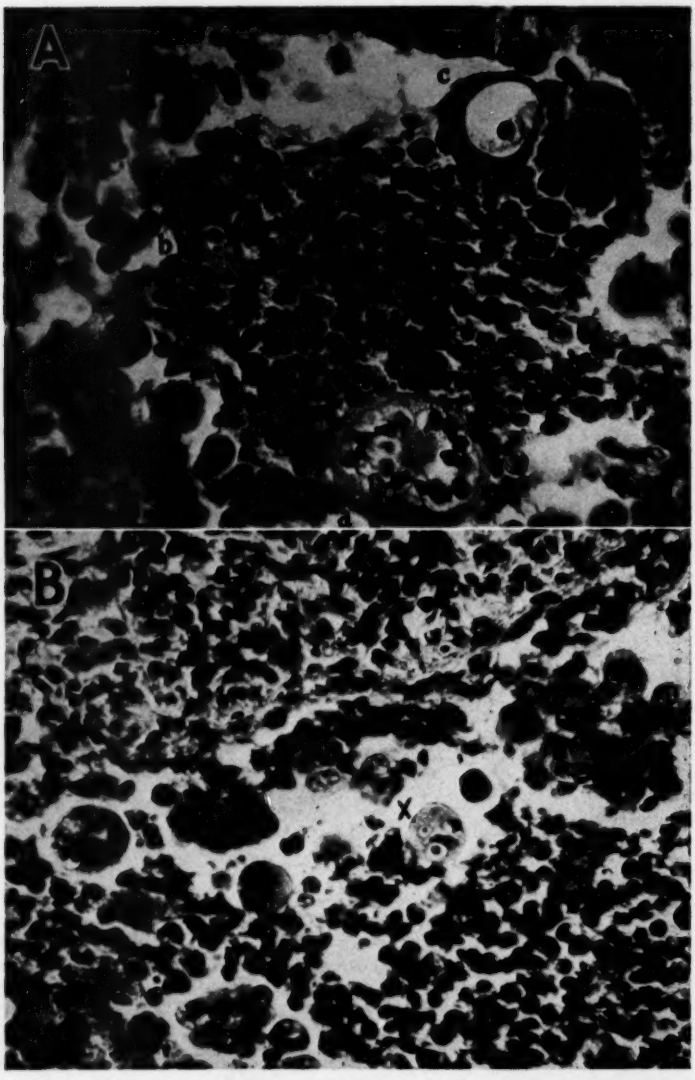

Fig. 3 (Case 1).—*A*, three giant cells. In one (*a*) the nuclei are arranged in a circular chain; in another (*b*) they are irregularly distributed, and the cytoplasm contains a number of small inclusion bodies; a third (*c*) contains a large vacuole; × 420. *B*, giant cells lying free in alveolar lumina. In one (*x*) two cytoplasmic inclusion bodies are seen; ×470.

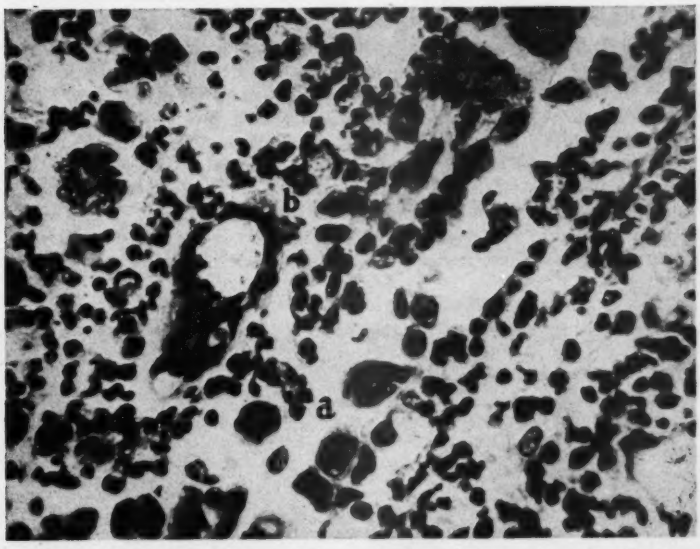

Fig. 4 (Case 1).—A bronchiole containing a number of giant cells (*a*). The lumen of a neighboring alveolus is filled by a large giant cell (*b*) with a wide vacuole containing cells and debris; ×530.

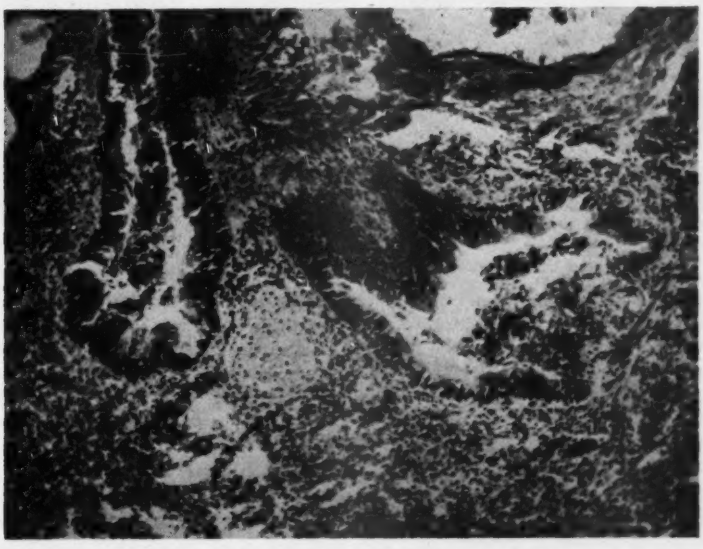

Fig. 5 (Case 2).—Hyperplastic changes and desquamation of bronchial epithelium; × 90.

Gross Findings at Autopsy.—Bronchopneumonic foci were scattered in both lungs. The remaining lung tissue was emphysematous. The liver and the spleen were congested.

Histological Findings at Autopsy.—Lungs: There were patches of interstitial infiltration alternating with large areas of atelectatic or emphysematous lung tissue (Fig. 1*A*). In many places foci of purulent bronchopneumonia were found. The alveoli in the atelectatic areas contained a large number of desquamated lining cells and some amorphous eosinophilic matter. The thickened septa contained congested capillaries and a number of histiocytes, plasma cells, and lymphocytes, and relatively few polymorphonuclear leucocytes (Fig. 1*B*). In some places the endothelial lining of the capillaries was swollen; here and there a few erythrocytes were found outside the capillaries within the septa. The lining cells of some alveoli were swollen, cuboidal, or polyhedric, and in a few places desquamated. Occasional multinucleated giant cells lined the alveoli or were found close to the alveolar walls (Fig. 2). Groups of giant cells were usually found within small areas of the sections, although the single cells were mostly at a distance from each other.

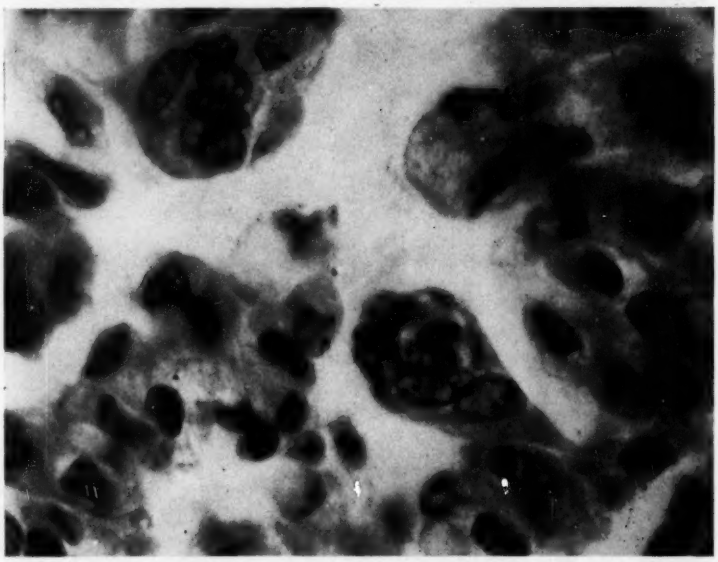

Fig. 6 (Case 3).—Pedunculated ("tennis racket") giant cells bulging into a bronchial lumen; × 1200.

The giant cells were between 20 and 70 μ in diameter, mostly round or oval, with somewhat irregular contours. They contained from 5 to 50 nuclei, some of which were oval and vesicular while others were shrunken, of irregular outline, and hyperchromatic. Either the nuclei were irregularly distributed in the cytoplasm or else they formed a circular chain lying about halfway between the center and the periphery of the cell. In some cells the cytoplasm surrounding the nuclei was clear, translucent, and sharply demarcated from the remaining granular cytoplasm (Fig. 3*A*). The cytoplasm of many giant cells contained inclusion bodies which were mostly round, homogeneous, and amphophilic, about 2 to 6 μ in diameter and surrounded by a clear halo (Fig. 3). The inclusion bodies did not take Noble's modification of Machiavello's stain for rickettsiae,[5] and they were stained by Feulgen's method with varying degrees of intensity. In a few places vacuoles of different sizes were contained in the cytoplasm of these cells. The largest vacuoles, up to 25 μ in diameter, pushed the cytoplasm and the nuclei to the periphery,

5. Meyer, K. F., in Diagnostic Procedures for Virus and Rickettsial Diseases, Ed. 2, New York, American Public Health Association, 1948.

lending to the cells a bird's-eye appearance (Figs. 3*B* and 4). The compressed cytoplasm of these cells was hyperchromatic.

The walls of some bronchi and bronchioles were thickened and infiltrated with a large number of the lymphocytes and histiocytes. The structure of the bronchial lining was changed: In some places there were patches of hyperplasia and metaplasia, with the formation of plaques made of several layers of columnar or stratified epithelium (Fig. 5).

In many bronchi and bronchioles there was a great deal of desquamation of the proliferated epithelial cells and accumulation in the lumina of a small number of histiocytes, lymphocytes, and granulocytes. In some bronchi giant cells of two different types were found: (*a*) cells similar to those found in the alveoli, with a peripheral arrangement of the nuclei, and (*b*) cells in the form of tennis rackets, which bulged with their thickened multinucleated parts into the lumina and were attached to the basal membranes with their peduncle-like thinner parts (Fig. 6). Inclusion bodies similar to those mentioned above were occasionally found in both types of giant cells.

Liver: There was marked congestion of the veins and sinusoids, and foci of slight periportal infiltration with lymphocytes and eosinophilic granulocytes were evident. The Kupffer cells were swollen.

Spleen: There was marked congestion in the spleen also. The sinus endothelial cells and the reticulum cells were hypertrophic. In many of them hemosiderin granules were found. The intersinusoidal tissue contained a moderate number of polymorphonuclear leucocytes and histiocytes with abundant homogeneous eosinophilic cytoplasm and plasma-cell-like nucleus. The Malpighian follicles were small and poorly delimited, with tiny irregular germinative centers.

Other Organs: No noteworthy changes were detected in the kidneys and the intestines, except for albuminoid degeneration in some renal tubules.

Case 2.—A 3-week-old boy, born prematurely, was admitted to the hospital on Jan. 14, 1950, with the diagnosis of dehydration. The infant had not taken food properly since birth and was loosing weight. The clinical examination upon admission revealed an undernourished infant, with a loose inelastic skin. The stools were fluid. The respiratory tract was clinically normal.

On Jan. 19 a few scattered rales were heard for the first time over the chest. On Jan. 20, the patient died suddenly after an apparently normal feeding.

During hospitalization the infant never had a fever. No laboratory examinations were performed. Treatment from the day of admission consisted in administration of penicillin, 200,000 units daily; streptomycin, 1 gm. daily; sulfadiazine, 1 gm. daily, and an intensive vitamin therapy.

Gross Findings at Autopsy.—There was an acute dilatation of the right cardiac ventricle. The lungs appeared grossly normal.

Histological Findings at Autopsy.—Lungs: The appearance was essentially similar to that in Case 1. There were, however, some minor differences: The bronchopneumonic foci were smaller and less widespread; the interstitial infiltration and the thickening of the septa were much more widespread and diffuse; large inclusion bodies were found in the cytoplasm of some giant cells (Fig. 7*A*), and in some areas there were intra-alveolar hemorrhages.

Spleen: The appearance of the spleen was essentially similar to that found in Case 1. In addition, there was some desquamation of the swollen lining cells of the sinuses and necrosis in the germinative centers of the Malpighian follicles (Fig. 7*B*). No other organs were available for histological examination.

Case 3.—A boy about 1 year old was brought dead to the hospital. No data as to prematurity were available. According to the parents, development had been defective since birth. The staff of the nursery in which the infant lived found him dead, without his having had any premonitory clinical symptoms.

Gross Findings at Autopsy.—The infant was 59 cm. long, undernourished, with depressed fontanelles. The skin was thin and inelastic. The lungs were prominent. There was a slight bilateral hemothorax, the pleural surfaces appeared granular, and a few fibrinous adhesions were found between the pleurae. All lymphatic tissues were hypertrophic.

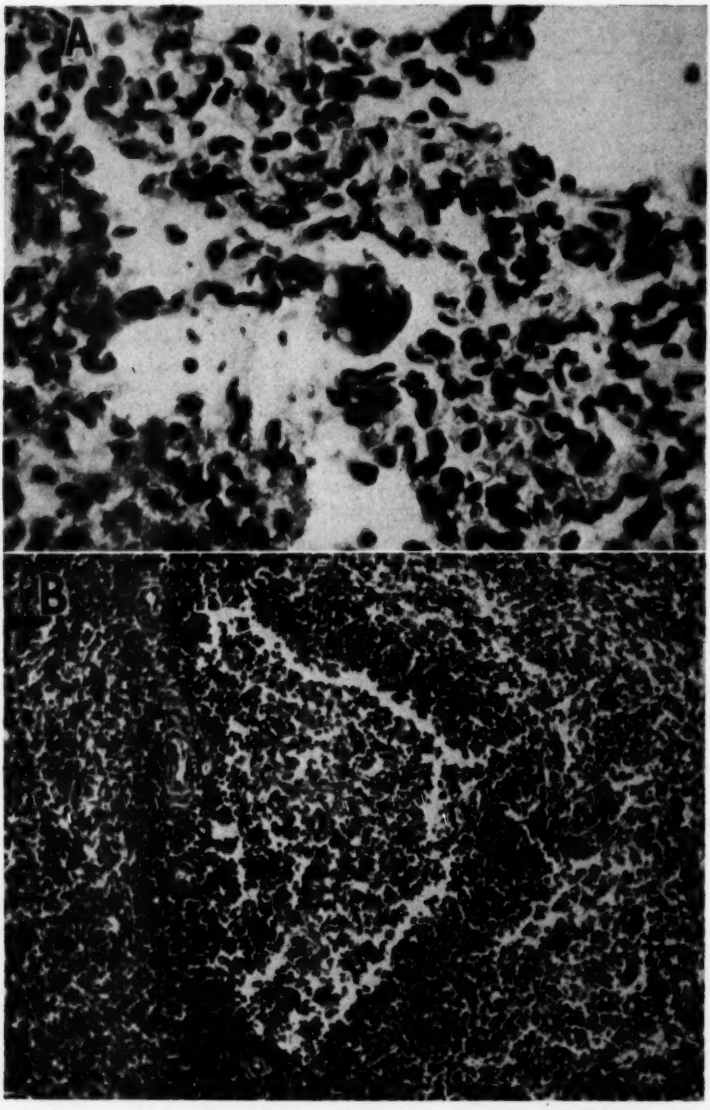

Fig. 7 (Case 2).—*A*, desquamated alveolar giant cell containing large inclusion bodies; × 530. *B*, necrosis in the germinative center of a splenic Malpighian follicle; × 150.

Histological Findings at Autopsy.—Lungs: The appearance was essentially similar to that found in the previous cases. In a few alveoli there was some slight infiltration with neutrophilic granulocytes. The foci of interstitial pneumonia were confluent in some places. The thickening of the septa was due in some places not only to the infiltration but also to interstitial hemorrhages. There were some intra-alveolar hemorrhages. Numerous giant cells, similar to those described in Case 1, were found lining the bronchi and the alveoli.

Spleen: The findings in the pulp were similar to those found in Case 1. The Malpighian follicles did not contain any germinative centers (Fig. 8).

Mesenteric Lymph Nodes: There was necrosis of the germinative centers.

Liver: Slight infiltration with lymphocytes and a few polymorphonuclear leucocytes was found in the portal spaces.

Kidneys: There was some albuminoid degeneration of the tubules.

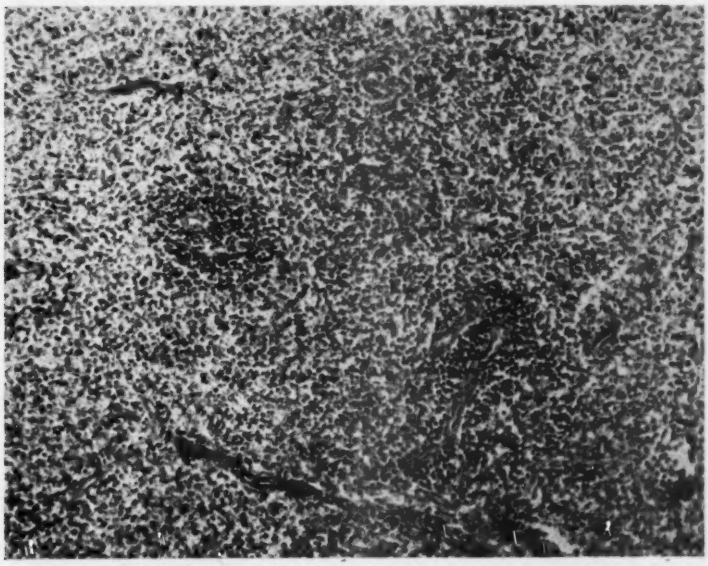

Fig. 8 (Case 3).—Section of spleen showing hyperplastic infiltrated red pulp and ill-defined, small Malpighian follicles; × 115.

CASE 4.—A 5-month-old boy was brought dead to the hospital. According to the parents the infant was born at full term, his weight was normal, and he was apparently healthy until the day of his death. Three hours after breast-feeding, during which no signs of illness were observed, the mother found the infant dead.

Gross Findings at Autopsy (Dr. E. Liban).—The lungs were emphysematous. Cut surfaces revealed prominent lobular structures. All the lymph nodes were hypertrophic; in the colon the lymph follicles were swollen, with superficial blood-stained erosions at their summits. The spleen was enlarged (20 gm.), with prominent Malpighian follicles on cut surfaces.

Histological Findings at Autopsy.—Lungs: The appearance was basically similar to that in the preceeding cases, except as follows: There was no evidence of a bronchopneumonic process anywhere. The interstitial pneumonia was confined to well-delimited patches of different sizes (Fig. 9*A*); a bronchus was usually found in the center of each patch, and the patches were surrounded by emphysematous areas. No hemorrhages were found, although there was marked congestion. In some places giant cells, similar to those described, were found lining the alveolar walls, often of adjoining alveoli (Fig. 9*B*) or lying free inside the lumina. A few giant cells were also found in the bronchi.

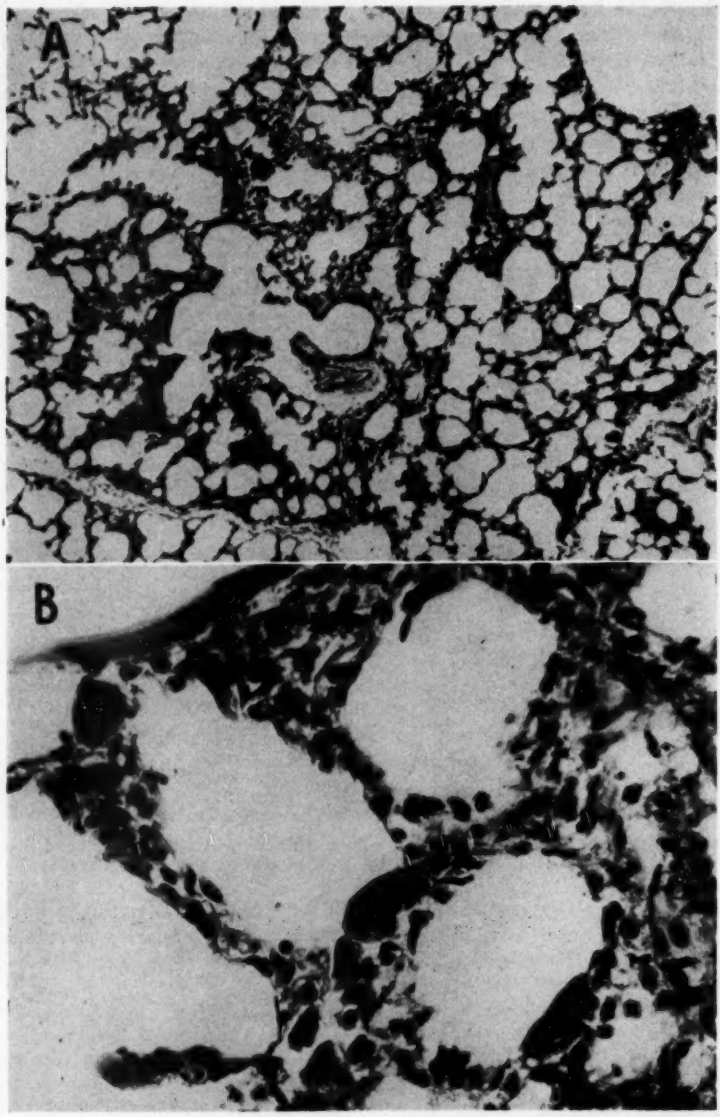

Fig. 9 (Case 4).—*A*, well-defined patch of interstitial pneumonia; × 48. *B*, three giant cells lining the walls of adjoining alveoli; × 530.

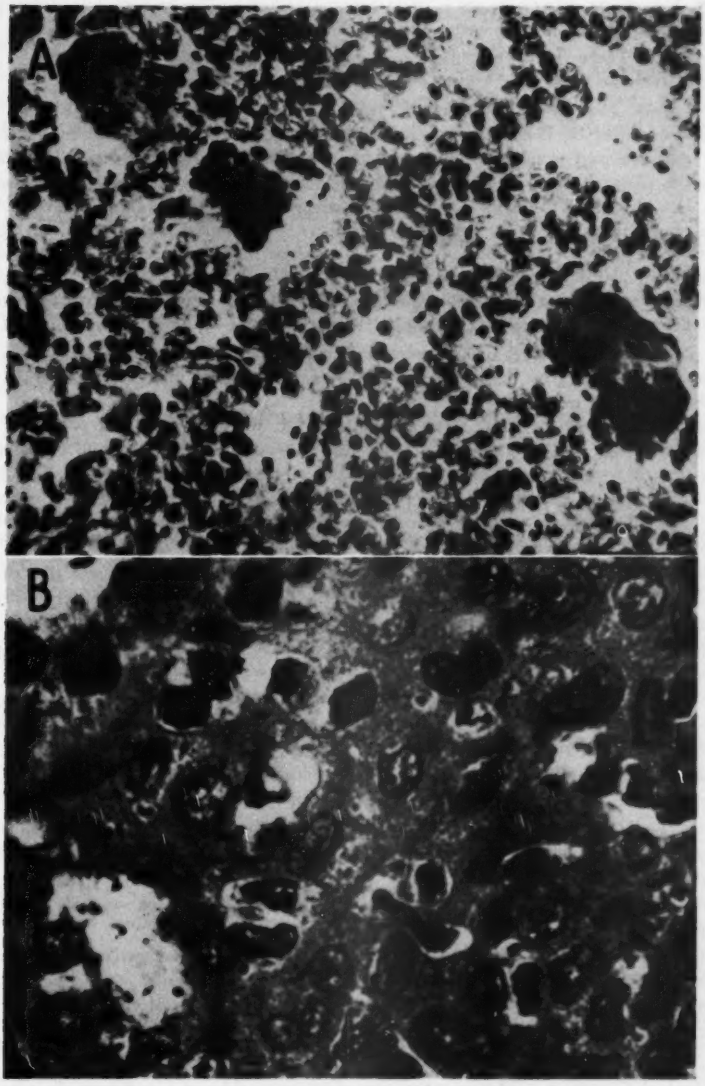

Fig. 10 (Case 5).—*A*, large multinucleated alveolar giant cells; × 360. *B*, degenerative changes and cytoplasmic inclusion bodies in tonsillar epithelium; × 500.

Liver: There was slight lymphocytic infiltration in the portal spaces.

Spleen: The appearance was similar to that in Case 2.

Intestines: The appearance of the lymph follicles was similar to that of the Malpighian follicles, i. e., there were necroses in the germinal centers. The mucosa was diffusely infiltrated with a large number of neutrophiles, eosinophiles, plasma cells, and histiocytes.

Adrenals: There was an extreme congestion in the blood vessels of the medulla.

Postmortem bacteriological cultures were negative.

CASE 5.—A 2-month-old boy, who was born at term, was admitted to the hospital for the first time on April 10, 1949. He was suffering from bilateral purulent otitis media and from severe diarrhea and vomiting. After restorative treatment, bilateral mastoidectomy was performed. After 50 days of hospitalization the infant was sent home, apparently cured.

On Dec. 16, 1949, the patient was readmitted to the hospital because of severe diarrhea of one week's duration and extreme dehydration. The clinical examination on admission failed to reveal any physical findings in the chest, except for a few scattered rales. The infant died suddenly on the third day after admission.

During hospitalization the temperature was subfebrile. Treatment consisted in administration of fluids and transfusion of 250 cc. of plasma.

Gross Findings at Autopsy.—The mucosa of the trachea and the large bronchi was rough, congested, and covered by thick mucus. In the smaller bronchi there were large amounts of greyish-red viscous matter.

The consistency of the lungs was rather firm. Cut surfaces revealed a prominent lobular structure. In some places there were small pale-gray peribronchial areas of consolidation.

The spleen was enlarged (25 gm.), tense, and of hard-elastic consistency. The lymphoid structures in the mouth, pharynx, and intestines were swollen and congested. Lymph glands elsewhere in the body were enlarged and congested. The esophagus mucosa was swollen and congested. There were hemorrhages in both adrenals.

Histological Findings at Autopsy.—Lungs: The appearances were essentially similar to those in case 1 except in the following respects. No bronchopneumonic process was found. The giant cells were usually rather large and contained numerous nuclei (Fig. 10*A*). They contained small inclusion bodies, but no vacuoles.

Tonsils: The lining epithelium showed degenerative changes. Clear vacuoles were seen either surrounding the nuclei or pushing them to the periphery. Many cells contained pyknotic nuclei. In a number of cells small eosinophilic or basophilic inclusion bodies were found in the cytoplasm (Fig. 10*B*). In the crypts there was marked epithelial desquamation.

Esophagus: The lining epithelium was partly desquamated. Inclusion bodies and changes similar to those observed in the tonsils were found in the epithelial cells.

Spleen: The red pulp was extremely congested; the sinusoids were dilated, and lined by swollen endothelium. The Malpighian follicles were small and ill-defined and did not contain germinative centers.

Lymphatic Tissue: In the alimentary tract the lymphatic tissue showed reticulum cell hyperplasia.

Adrenals: Hemorrhages were found in the reticular zone of the cortex, spreading into the fasciculate and glomerular zones, and in places involving the medulla.

No contributory findings resulted from postmortem bacteriological cultures.

RESULTS

Clinical Features.—The onset of the disease could not be accurately established in any of the cases. The three patients who were given a physical examination presented clinical evidence of bronchial involvement without consolidation. The same patients also suffered from diarrhea and were markedly dehydrated, and in two of them there was evidence of a nonpurulent pharyngitis. The temperature was either normal or subfebrile. The two patients who were treated with sulfonamide drugs, penicillin, and streptomycin did not respond to the therapy.

Sudden Death.—Three of the five infants died suddenly. Two of them died at home without any apparent previous signs of illness. One who was in the hospital because of dehydration and diarrhea also died without any premonitory symptoms.

Pathological Findings in the Lungs.—In all cases the histological examination of the lungs revealed congestion, patchy interstitial pneumonia, metaplastic changes and desquamation of the bronchial and alveolar lining, and the presence of epithelial giant cells with cytoplasmic inclusions. There were areas of emphysema and areas of atelectasis. In all five cases the bronchial lumina contained desquamated bronchial epithelium.

The interstitial infiltration in the single patches was usually of uniform intensity throughout each patch. There was no evidence of spread of the process from the infiltrated peribronchial tissues into the lobular stroma. The purulent intra-alveolar exudate found in three cases represents, in our opinion, a complication superimposed on the primary disease, as the development of infections in the lung is generally believed to be enhanced by the action of other noxious agents.[6]

These findings were complicated by intra-alveolar and interstitial hemorrhages in two cases.

Giant Cells.—The giant cells found in the lungs were pleomorphic. In some bronchi the number of lining cells seemed not to have increased, as each of the "tennis racket" cells was attached to the basal membrane by a thin peduncle clearly separated from the adjoining cells. This finding suggests that these giant cells formed as a result of multiple nuclear divisions, without corresponding division of the cytoplasm. In other places, mainly in bronchioles and alveoli, there were some giant cells in which the nuclei still had the original arrangement of the individual lining cells. They appeared to have been derived from fusion of the latter cells. In either case it seems obvious that the giant cells originated from the lining epithelium.

Inclusion Bodies.—The inclusion bodies found in the epithelia of the lungs varied with regard to size and staining characteristics. They were mostly amorphous and solid masses, 2 to 7 μ in diameter, round, and usually surrounded by a clear halo. The inclusions were found only in the cytoplasm. Some of them were relatively basophilic; others appeared eosinophilic. While in most of them the Feulgen reaction was negative, in some it was positive. Some cells contained several inclusions of different sizes and shapes.

Pathological Findings in Other Organs.—In all cases there was evidence of lymphatic tissue involvement. In the spleen, in the lymph nodes, and in all the lymphatic structures of the alimentary tract examined, the lymphatic follicles were poorly defined and either hypertrophied or atrophied, with necrotic germinative centers or without any such centers. In all cases the spleen was congested, and there was hypertrophy of the reticuloendothelial cells. In four cases, the splenic pulp was diffusely infiltrated with histiocytes and granulocytes. In the only case in which tonsils and esophagus were examined histologically, degenerative changes and cytoplasmic inclusion bodies were found in the epithelial cells. In the adrenals there was a massive hemorrhage involving the inner part of the cortex and the

6. W. E. Nelson: Mitchell-Nelson Textbook of Pediatrics, Ed. 4, Philadelphia, W. B. Saunders Company, 1945, p. 777.

medulla in one case; in another case there was an extreme congestion of the capillaries. In the remaining three cases the adrenals were not examined histologically.

COMMENT

The clinical and pathological findings indicate that the five cases described represent a disease entity characterized by the features summarized above. This entity seems to correspond closely to the various recent reports on giant cell pneumonia, referred to as Hecht's disease. Kromayer [7] reported the findings in six autopsies of children who died of pneumonia following measles or pertussis. Histological examination of the lungs revealed interstitial pneumonic processes with epithelial giant cells. This author accurately described the formation of the epithelial giant cells in two different ways, i. e., fusion of epithelial cells or division of nuclei without corresponding cytoplasmic fission. In 1910 Hecht [8] described another 27 cases of similar appearance, in most of which the condition followed measles or whooping cough.

The recent reports on pneumonia following measles correspond to the descriptions of Kromayer and Hecht, and in addition another specific change was reported in 1931 in the peribronchial lymphatic tissue, as well as in the lymphatic tissues throughout the body, i. e., the Warthin-Finkeldey giant cells (Corbett [9]). Under the term Hecht's disease recent authors [10] described a pulmonary condition which is characterized by the presence of epithelial giant cells in the lungs, but in which there is no clinical history of measles, and no Warthin-Finkeldey giant cells are found.[11]

Our cases correspond to the last-mentioned descriptions, for which in our opinion the term interstitial giant cell pneumonia is adequate. The origin of interstitial giant cell pneumonia has been much debated. Friedlaender in 1876 [12] obtained similar histological changes in the lungs of rabbits by section of both recurrent laryngeal nerves. Hecht was able to reproduce these changes by intratracheal injection of various chemicals. Both authors considered the changes as reaction to foreign matter. Chown [13] thought the disease might be caused by vitamin-A deficiency. Other authors suggested a virus origin and believed that

7. Kromayer, E.: Über die sogenannte Katarrhalpneumonie nach Masern und Keuchhusten, Virchow's Arch. path. Anat. **117**:452, 1889.

8. Hecht, V.: Die Riesenzellenpneumonie in Kindesalter, Beitr. path. Anat. u. allg. Path. **48**:263, 1910.

9. Corbett, E. U.: The Visceral Lesions in Measles, Am. J. Path. **21**:905, 1945.

10. Pinkerton, H.; Smiley, W. L., and Anderson, W. A. D.: Giant Cell Pneumonia with Inclusions: A Lesion Common to Hecht's Disease, Distemper and Measles, Am. J. Path. **21**:1, 1945. Palmer, H. D.: Clinicopathologic Conference, Am. J. Clin. Path. **18**:659, 1948. Gunn, F. D., in Synopsis of Pathology, edited by W. A. D. Anderson, Ed. 2, London, Henry Kimpton, 1946.

11. The term Hecht's disease is a misnomer. Hecht described the histological findings in the lungs of infants with pneumonia following measles and whooping cough.

12. Friedlaender, C.: Experimentaluntersuchungen über chronische Pneumonie und Lungenschwindsucht, Arch. path. Anat. **68**:325, 1876.

13. Chown, B.: Giant Cell Pneumonia of Infancy as a Manifestation of Vitamin A Deficiency, Am. J. Dis. Child. **57**:489 (March) 1939.

interstitial giant cell pneumonia, pneumonia following measles, and canine distemper might be related.[14]

The study of our cases allows us to draw the following conclusions as to the origin of interstitial giant cell pneumonia.

(*a*) There was no clinical or pathological evidence of inhalation of chemical irritants.

(*b*) While a possible relationship between viral metabolic activity and vitamin-A deficiency, according to the opinion of Pinkerton and his co-workers, is a definite possibility, there was no clinical evidence of vitamin-A deficiency in our patients, and intensive vitamin therapy was of no avail.

(*c*) We do not consider our cases as representing pneumonia following measles, since there was no clinical evidence suggestive of measles, nor were there changes in the lymphoid tissues similar to those described in measles (such as the Warthin-Finkeldey cells).

(*d*) The relationship of giant cell pneumonia to canine distemper has no clinical or epidemiological basis as yet. In none of our cases was there any evidence of direct contact with dogs.

(*e*) There seems to be some evidence in favor of viral origin of interstitial giant cell pneumonia in general and of our cases in particular. Such a view is supported by the presence of intracellular inclusion bodies, by the epithelial proliferation and metaplasia, by the interstitial type of the pneumonic process, and by the noncontributory bacteriological findings.

Interstitial giant cell pneumonia is similar to the disease called virus pneumonia of infants, plasma-cell pneumonia, or *frühgeburten Pneumonie,* both clinically and pathologically in all respects but one, namely, the presence of giant cells. We were impressed by the fact that both in Jerusalem and in Rosh Haayin the cases occurred in between other cases of interstitial pneumonia, clinically and pathologically similar, but in which no giant cells were found. The number of giant cells in the different cases varied considerably. The fact that in some of our cases, just as in some other cases of interstitial pneumonia, interstitial and intra-alveolar hemorrhages were found also strengthened the similarity.

It is a well-known fact that the type of reaction of tissues to infectious agents depends on various factors, such as the amount of the noxious agent, environmental conditions, and the immunological state of the host. Muckenfuss,[15] who studied experimental vaccine of virus pneumonia in rabbits, arrived at similar conclusions. In accordance with this, we believe that the relative intensity of the vascular changes in interstitial pneumonia of children, the amount and character of the infiltration, and the character of the hyperplastic response of the lining cells might correspond either to quantitative differences in the host-noxious-agent relation or to different stages of a single process. We therefore suggest that interstitial giant cell pneumonia and virus pneumonia of infants represent a single disease entity caused by virus.

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14. Corbett.[9] Pinkerton, Smiley, and Anderson.[10]

15. Muckenfuss, R. S.; McCordock, H. A., and Harter, J. S.: A Study of Vaccine Virus Pneumonia in Rabbits, Am. J. Path. **8**:63, 1932. McCordock, H. A., and Muckenfuss, R. S.: The Similarity of Virus Pneumonia in Animals to Epidemic Influenza and Interstitial Broncho-Pneumonia in Man, ibid. **9**:221, 1933.

It is possible that giant cell pneumonia is not such a rarity as the paucity of pathological reports seems to indicate. The apparent rarity might be due to the frequent presence of secondary invaders, which masks the original picture, and to the possibility that autopsy is rarely performed at the giant-cell stage of the disease.

SUMMARY AND CONCLUSIONS

The clinical and pathological changes in five cases of interstitial giant-cell pneumonia, misnamed Hecht's disease, are described.

Besides the usual findings of interstitial pneumonia, there was clinical and pathological evidence of a generalized lymphatic-tissue involvement.

Three of the five patients died suddenly, without premonitory symptoms.

Epithelial giant cells were found in the alveoli and bronchi. They contained cytoplasmic inclusion bodies.

Interstitial giant cell pneumonia is considered to be due to virus, and its possible relationship to so-called virus pneumonia of infants, plasma-cell pneumonia, and *frühgeburten Pneumonie* is discussed.

INCIDENCE OF SKIN-TEST REACTIONS AMONG CHILDREN IN THE PITTSBURGH DISTRICT

I. Histoplasmin

ANNA-MARY CARPENTER, Ph.D.
AND
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PITTSBURGH

BECAUSE of the geographic location of Pittsburgh, one might anticipate the existence of histoplasmosis. Not only are the city and environs situated between two areas in which there is a high incidence of skin-test reactions, namely, Maryland and Ohio, but also they are located at the convergence of three major rivers. Although the city proper is highly industrialized, typical rural areas are adjacent to the city limits. Clinicians in the area are well aware of the implications of the geographic location as related to histoplasmosis, but definite knowledge of incidence is lacking. Only a few positive skin reactions have been obtained in the area, and no active clinical case, to our knowledge, has been reported. With this in mind, we began to gather data among patients of the Children's Hospital.

Because the literature covering epidemiologic studies in histoplasmosis in the United States has been reviewed by Shaw, Howell, and Weiss,[1] only references pertaining to Pennsylvania are tabulated here. To these data is added herewith this first paper on reactors from the western part of the state where no mass testing has been done. The series constitutes, as well, the greatest number of tests on infants and children reported for the state.

SELECTION OF PATIENTS

The first group of patients included in the study comprised some 150 infants and children for whom, over a period of two years, a skin test was requested specifically by attending pediatricians. In a number of cases there were signs and symptoms which had suggested to the physician that histoplasmosis must be considered.

The second group was composed of 311 patients admitted consecutively to the medical services of the hospital from August to November, 1950. Ages of these subjects ranged from newborn premature infants to children approaching their 15th birthday (Fig. 1). Among the 284 children for whom there are complete data, there were 56 Negro and 228 white patients; boys numbered 154 as opposed to 130 girls. The wide variety of clinical diagnoses were those generally encountered on a medical service, but in no case was clinically active histoplasmosis recorded as the chief diagnosis.

From the Departments of Pathology and Pediatrics, University of Pittsburgh and Children's Hospital.

1. Shaw, L. W.; Howell, A., Jr., and Weiss, E. S.: Biological Assay of Lots of Histoplasmin and the Selection of a New Working Lot, Pub. Health Rep. **65**:583, 1950.

Concurrently 4 adults chosen at random, as well as 10 patients and 3 siblings of patients who were reactors, were tested. These totaled 15 adults and 2 children.

MATERIALS

Histoplasmin antigen for the project was of lot H-40, procured in April, 1948, from Dr. Arden Howell, mycologist of the United States Public Health Service. When this supply had been exhausted, after 146 tests in the series, 1 ml. of lot H-42 was sent to us by Forrest W. Cross, Senior Sanitarian of the United States Public Health Service. Lot H-40 was employed in 1:1,000 dilution in phenolized sterile isotonic sodium chloride solution; lot H-42, as used in 1:100 dilution, corresponds in antigenicity.[1]

Concomitant with injection of histoplasmin, Wyeth's old tuberculin was injected into the right arm of each patient. The results are the subject of the second paper in this series.[2]

New syringes and 26-gauge needles were kept separate for the specific skin tests mentioned above. They were cleaned daily in dreft® solution and rinsed with distilled water. In addition, once weekly they were washed with a cleaning solution of potassium dichromate and sulfuric acid. Daily sterilization was by autoclaving.

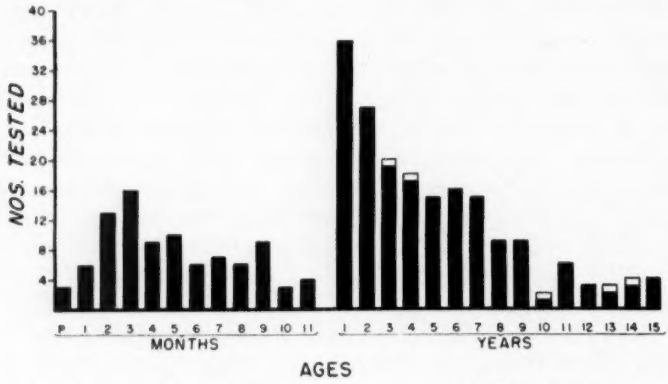

Fig. 1.—Age distribution of children on whom skin tests with histoplasmin were done; five clear squares represent positive reactors.

PROCEDURE

One-tenth milliliter of histoplasmin antigen was injected intradermally on the volar surface of the left arm after the area had been sponged with 70% alcohol. Arms of all patients were examined by us after 24 and 48 hours. Reactions were considered positive when, at 48 hours, induration measured 5 mm. or more in diameter.

Patients who showed a positive reaction to histoplasmin were tested on the opposite arm to verify the readings. When a reaction to the first test exceeded 10 mm., the second test was done with a 1:500 dilution of lot H-42 antigen. Serum from each patient who reacted to histoplasmin was sent to Miss Charlotte Campbell at the Army Medical Research and Graduate School for complement fixation and collodion agglutination studies. These patients also received, intradermally, 0.1 ml. of blastomycin (lot B-7, 1:1,000, obtained from Dr. Howell) to elicit cross reactions.

Plane roentgenograms of the thorax in lateral and posterior-anterior projections were made for patients with positive reactions to skin tests and on the majority of the children whose reactions were negative to the antigen. All roentgenograms were interpreted by a roentgenologist and by one of us (P. D. S.).

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2. Carpenter, A. M.; Spino, P. D., and Hadden, J. C.: Incidence of Skin-Test Reactions Among Children in the Pittsburgh Area: II. Tuberculin, A. M. A. Am. J. Dis. Child., this issue, p. 598.

RESULTS

Of 461 children tested, there were five positive reactors to histoplasmin; these five patients had negative reactions to tuberculin. In four of the five patients intrathoracic calcifications were seen. Three of the five children were found as a result of request for testing, while two were among the group admitted routinely to the hospital. All five children were white; four were girls. Four of the five reactors were discharged from the hospital with an undetermined diagnosis; thus they constituted definite diagnostic problems. Two children were referred to this hospital from out of the state, one from Ohio and one from Ontario, Canada; the other three were residents of Allegheny County, Pa.

Chest roentgenograms of four of the five positive reactors revealed nodular intrathoracic calcifications which varied in size. The site of pathema ranged from parenchymal to hilar. In two cases the calcifications were isolated single lesions, whereas in two others they were multiple. Although we were unable to verify clinical evidence with immunologic data, it is believed that N. H. (Case 1), who demonstrated no calcification in the chest, may have been in a more acute phase of the disease.

Results of complement fixation and collodion agglutination studies were negative for four children with positive skin-test reactions. Data are lacking for the fifth patient, R. A. (Case 4), because blood was not obtained. The indication that none of these patients was in the acute phase of the disease is verified by the presence of pulmonary calcifications.

TABLE 1.—*Summary of Findings for Five Reactors to Histoplasmin*

	Age, Yr.	Histoplasmin*	Tuberculin	Calcification	Blastomycin	Allergy	Joint Pain	Father	Mother	Siblings	State
N. H.	3	+Q	—	Bone	+	Milk	+	H— TB+	H+ TB—	....	Pa.
J. I.	4	+Q	—	Thor	—	.....	+	H—	H—	H—	Pa.
M. M.	10	+Q	—	Thor	—	.....	+	H+	H+	....	Canada
R. A.	13	+T	—	Thor	—	.....	+	H+	H—	....	Ohio
W. H.	14	+T	—	Thor	+	Wheat	+	H+ TB—	H+ TB+	H+, H+	Md.

* Q indicates request; T indicates routine.

Members of the families of all positive reactors were tested with histoplasmin antigen. In four of the five cases at least one additional member of the family had a positive reaction. Of 15 adults and 2 children, 9 adults and 1 sibling had positive reactions to histoplasmin. Two of these adults were among the four chosen at random. The seemingly high incidence among adults was expected, inasmuch as the sample was skewed to families of reactors.

Response to histoplasmin persisted longer than 48 hours, sometimes as long as three months. Induration was well beyond the 5-mm. size generally accepted as a positive reaction, and marked erythema accompanied all positive reactions. Of the total 15 positive skin reactors seen in this series, three persons had necrosis of the area of activity.

COMMENT

The specificity of any antigen is a subject of interest. Emmons and his co-workers [3] first questioned the specificity of histoplasmin when he demonstrated cross

3. Emmons, C. W.; Olson, B. J., and Eldridge, W. W.: Studies of the Role of Fungi in Pulmonary Disease: I. Cross Reactions of Histoplasmin, Pub. Health Rep. **60**:1383, 1945.

reactions with blastomycin which are now commonly cited. Howell,[4] however, has reported that the percentage and size of cross reaction is dependent on the dosage of antigen. Where critical titers of antigen are used, the response is smaller with heterologous antigen. Of the five subjects with positive results in this series, three had negative reactions to blastomycin, while in the two patients who showed cross reaction to blastomycin, the histoplasmin skin reaction was larger than the blastomycin reaction. These two patients also had associated allergic manifestations, one to milk, the other to wheat (Table 1).

It is worth more than passing notice that for each of the five patients in whom a positive reaction to histoplasmin was elicited there was a history of joint pain as the presenting symptom. This may be a coincidence, but to our knowledge no mention had been made of the symptom in the pediatric literature. Although the symptom

TABLE 2.—*Incidence of Reactors in Pennsylvania and Eastern Ohio As Reported in the Literature*

Author	Series	No. Tested	No. Histoplasmin +	Per Cent Histoplasmin +	Per Cent Tuberculin +	Per Cent with Calcification
Palmer *	.....	737	87	11.8	....	....
Palmer *	Philadelphia student nurses	883	121	13.7	....	....
Christie and Peterson [7]	Pennsylvania students at Vanderbilt University	39	8	20.5	23.1	35.9
Zwerling and Palmer †	Philadelphia nurses	...	..	14.4	26.6	7.4
Krug and Glenn ‡	Pennsylvania students at Pennsylvania State College	2,152	..	11.2	20.0	....
Groover and others §	Soldiers from Pennsylvania with calcification	56	27	48.0	44.0	....
Beadenkopf and others ‖	Pennsylvania students at University of Chicago	161	26	16.1	....	10-14
Smith and others ¶	Pennsylvania personnel in Air Force	201	40	20.0	....	....
Palmer *	Nurses from eastern Ohio	118	33	28.0	....	....
Prior and Allen **	Nurses, Ohio State University freshmen, Area 2	...	..	18.1	21.0	....
Hudson and others ††	Ohio college students	2,277	899	39.2	8.4	17.6

* Palmer, C. E.: Pub. Health Rep. **60**:513, 1945.
† Zwerling, H. B., and Palmer, C. E.: Radiology **47**:59, 1946.
‡ Krug, E. S., and Glenn, H. R.: J. Lancet **68**:206, 1948.
§ Groover, M. E., Jr., and others: Arch. Int. Med. **80**:496 (Oct.) 1947.
‖ Beadenkopf, W. G., and others: Pub. Health Rep. **64**:17, 1949.
¶ Smith, C. E., and others: Am. J. Pub. Health **39**:722, 1949.
†† Hudson, E. H.; Moore, F. R., and Phillips, E. A.: J. Lancet **68**:142, 1948.

is reported as having occurred among adults,[5] it is established that the symptomatology of histoplasmosis differs in children and adults.[6]

Table 2 summarizes the data in the literature on the incidence of positive reactors in Pennsylvania and eastern Ohio. These reports represent an older age group than our series, and it is known that histoplasmin sensitivity increases with age.[7] Figure 2, a map of the tristate area, shows a 9.4% reactor rate for the state of Pennsylvania as a whole except for the south central counties where the percentage rises to 33.[8]

4. Howell, A., Jr.: Studies of Fungus Antigens: I. Quantitative Studies of Cross-Reactions Between Histoplasmin and Blastomycin in Guinea Pigs, Pub. Health Rep. **62**:631, 1947.

5. Reimann, H. A., and Price, A. H.: Histoplasmosis in Pennsylvania: Confusion with Sarcoidosis and Experimental Therapy with Bacillomycin, Pennsylvania M. J. **52**:367, 1949.

6. Iams, A. M.; Tenen, M. M., and Flanagan, H. F.: Histoplasmosis in Children: Review of Literature, with Report of a Case, Am. J. Dis. Child. **70**:229 (Oct.) 1945.

7. Christie, A., and Peterson, J. C.: Histoplasmin Sensitivity, J. Pediat. **29**:417, 1946.

8. Palmer, C. E.: Geographic Differences in Sensitivity to Histoplasmin Among Student Nurses, Pub. Health Rep. **61**:475, 1946.

Eastern Ohio bordering on our area has about 18% positive reactors to histoplasmin.[9]

Because no asymptomatic children were tested, this study does not represent a cross section of the youth of the area. It is planned, however, to test school children and well babies at a later date to support the epidemiologic data presented for the Pittsburgh district.

SUMMARY

Routine tests with histoplasmin on 311 children admitted consecutively to the medical service of Children's Hospital, Pittsburgh, resulted in two positive reactions, whereas among 150 patients for whom the test was requested, there were three positive results.

In four of the five cases in which there was a positive reaction to histoplasmin there was coexisting intrathoracic calcification.

Joint pain was the presenting symptom in each of the five positive reactors.

In this study the incidence of positive reactions to skin tests with histoplasmin is less than 2%.

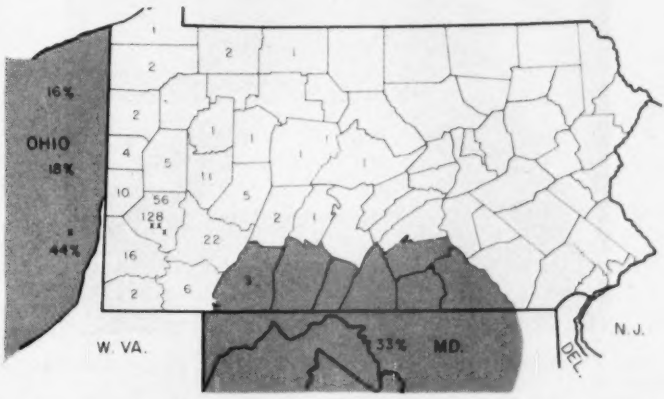

Fig. 2.—Map of Pennsylvania showing number of patients tested in the various counties; x denotes positive reactors; shaded areas and percentage figures for adjoining states are those reported in the recent literature.

It is of interest that positive skin-test reactions were elicited in nine adults and one sibling as well.

APPENDIX

REPORT OF CASES

CASE 1.—N. H., a 3-year-old white girl from Pittsburgh, manifested a generalized maculopapular rash at the age of 6 months. Gradually, the rash became more severe and soon was accompanied by tender joints of the legs, failure to walk, polydipsia, and polyuria. The diagnosis of polyneuritis and allergy to milk was made. Symptoms disappeared during a two-day hospital stay.

All symptoms reappeared in October, 1950, following an upper respiratory infection. A more complete history at this time revealed prolonged overdosage of vitamin A. Examination showed

9. Prior, J. A., and Allen, M. F.: Geographic Distribution of Histoplasmin and Tuberculin Reactors Among Ohio State University Freshmen and Student Nurses Training in Columbus, Ohio Hospitals, Pub. Health Rep. **62**:1608, 1947.

the liver to be 2½ fingerbreadths below the right costal margin and the tip of the spleen to be palpable. The white blood cell count was elevated to 15,000. Histoplasmin skin-test reaction measured 15 by 7 mm., blastomycin, 6 by 7 mm.; the reaction was negative to 1.0 mg. of old tuberculin. Complement fixation and collodion agglutination reactions were negative. Roentgenograms showed no abnormalities of the chest, but increased cortical thickening, typical of vitamin-A intoxication, was noted in the bones of the legs and the arms. The patient had at no time traveled outside Pennsylvania. The mother was histoplasmin-positive and tuberculin-negative. The father was histoplasmin-negative but had a positive reaction to 0.01 mg. of tuberculin.

CASE 2.—J. I., a 4-year-old white boy, had pain and a limp of the left knee which persisted for three weeks. Findings from physical examination included a generalized lymphadenopathy and a liver edge palpable to 2 fingerbreadths. Right axillary lymph-node biopsy revealed reactive hyperplasia. There was an eosinophilia of peripheral blood to the extent of 4 to 6%. Microscopic and cultural studies of bone marrow were noncontributory. The chest roentgenogram (Fig. 3) revealed infiltration of both upper lobes, with calcification at the hilar areas. Cultures of bronchial secretions revealed no fungi. The patient, born and reared in Pittsburgh, has not been out of the state. The mother, the father, and a 7-year-old brother were histo-

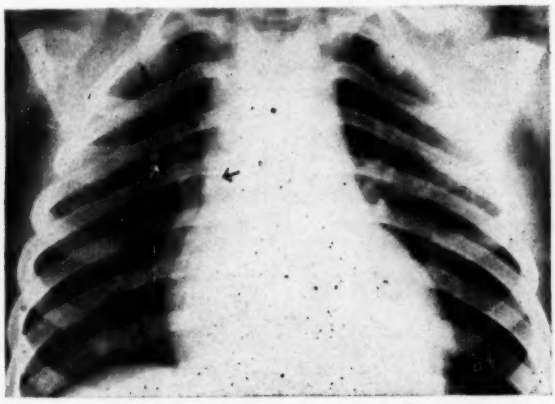

Fig. 3 (Case 2).—Roentgenogram of the chest showing infiltration of both upper lobes, with calcification at the hilar areas.

plasmin-negative. The father, a former serviceman, had seen duty in southeastern United States and in Europe. The brother had cervical adenopathy. Complement fixation and collodion agglutination reactions were negative in each member of the family. These immunologic studies were made by Dr. M. Furculow, United States Public Health Unit, University of Kansas, Kansas City, Mo. The diagnosis was histoplasmosis, nonauthenticated, with subacute synovitis of the left knee.

CASE 3.—M. M., a 10-year-old white girl, was referred from St. Thomas, Ontario, Canada, because of knee-, ankle-, and elbow-joint pains, in addition to abdominal and chest pains. Symptoms were of two years' duration. A great uncle had died of tuberculosis in 1949. A roentgenogram of the patient's chest revealed mediastinal enlargement, a calcified nodule in the right upper lobe, and calcification at the right hilus. The roentgenogram in Figure 4 was selected to reveal early changes identical to those seen in tuberculosis. The leucocytes were increased to 18,450. Sedimentation rate was 40 mm. per hour. Occasional spikes of fever to 102 F. (rectal) occurred. Bone-marrow studies were noncontributory. The histoplasmin reaction was positive; blastomycin and tuberculin reactions were negative, as were the complement fixation and collodion agglutination reactions. Both the father and the mother showed positive reactions to histoplasmin. No definite diagnosis was reached.

Fig. 4 (Case 3).—Roentgenogram showing early changes identical with those seen in tuberculosis.

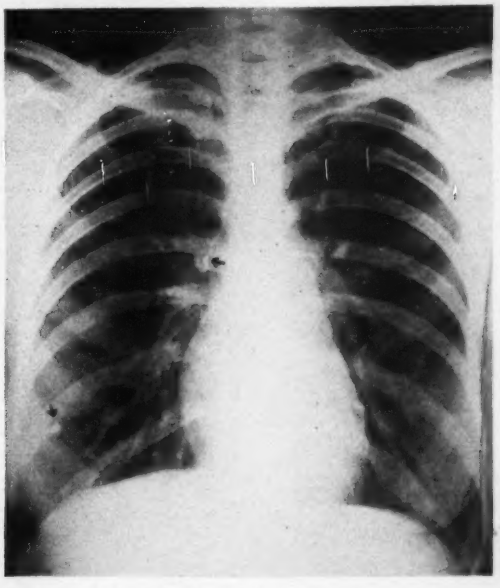

Fig. 5 (Case 5).—Chest of histoplasmin-positive, tuberculin-negative mother, showing calcification of the lung.

Fig. 6 (Case 5).—Calcification of the lung of the mother.

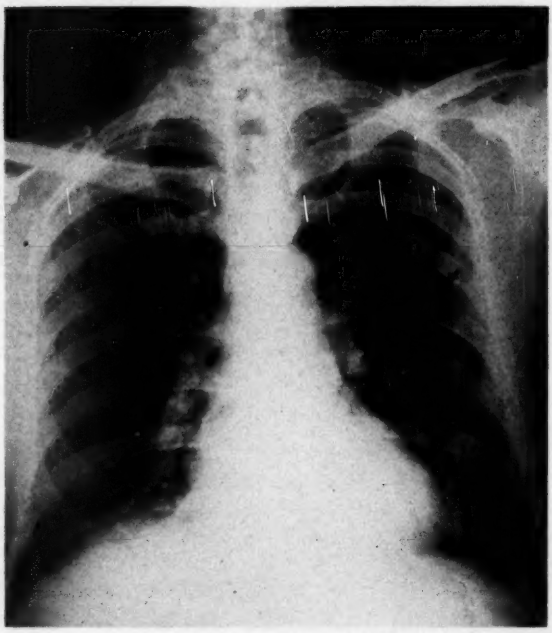

Fig. 7 (Case 5).—Chest of the father, showing small disseminated intrathoracic calcifications.

CASE 4.—R. A., a 13-year-old white girl from a farm in Cadiz, Ohio, was referred because of recurrent shoulder, knee, and elbow pains of one year's duration. Symptoms were accompanied by excessive fluid intake, diarrhea, and vomiting. Pertinent clinical findings included hypertension (blood pressure, 160/90 mm. Hg), a double-kidney pelvis, and sinus tachycardia. Laboratory findings were essentially normal. The area of the positive reaction to the histoplasmin skin test measured 50 by 40 mm., but the reactions to the tuberculin and blastomycin skin tests were negative. The chest roentgenogram revealed enlarged hilar nodes with calcification in the right side of the chest. The mother's reaction to histoplasmin was negative, but the father's was positive. The child, who was discharged with no definite diagnosis, is being followed by a cardiologist.

CASE 5.—W. H., a 14-year-old girl from Indianola, Pa., was admitted to the hospital with the chief complaint of intermittent pain and swelling of the finger joints and right knee during the preceding seven-month period. Five members of the family had rheumatoid arthritis or rheumatic fever. Two sisters and one brother of the patient were well. Physical examination revealed swollen, tender metacarpal and knee joints. The laboratory findings were essentially normal with the exception of a white blood cell count of 16,000. Histoplasmin (60 by 40 mm.) and blastomycin (15 by 15 mm.) skin-test reactions were positive; the tuberculin reaction was negative. The lung roentgenogram showed small calcifications of the right lower side of the chest, but roentgenograms of the involved joints were normal.

The mother, who was histoplasmin-positive and tuberculin-positive, has considerable calcification of the lung (Figs. 5 and 6). She told us that she had previously been an enigma to her physician because, although the tuberculin reaction was negative, pulmonary calcification was present. The father's reaction was positive to histoplasmin but negative to tuberculin. His roentgenograms showed small disseminated intrathoracic calcifications (Fig. 7). A brother who had been in Panama was histoplasmin-positive. A 12-year-old sister had an equivocal reaction to histoplasmin at 72 hours. Complement fixation and collodion agglutination reactions of all members of the family were negative. The family lives in Allegheny County in western Pennsylvania, but they have spent considerable time on a farm in Maryland. Although rheumatoid arthritis was considered, no definite diagnosis was made.

INCIDENCE OF SKIN-TEST REACTIONS AMONG CHILDREN IN THE PITTSBURGH DISTRICT

II. Tuberculin

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AND
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FROM TIME to time, it is valuable to reassess the percentage of positive reactors to tuberculin, particularly because it is known that such epidemiologic data are not static. This report of tuberculin testing among a large group of children in the Pittsburgh area confirms the value of routine tuberculin testing. Two unsuspected active cases were brought to light, a number of inactive cases were revealed, and, in many instances, a positive reaction in a child has led to the discovery of a tuberculous subject among adults.

SELECTION OF PATIENTS

From August to December, 1950, four hundred fifty-three patients admitted consecutively to the medical services of the hospital were given skin tests with tuberculin. Of these, 59 patients were tested with tuberculin alone, 293 were tested simultaneously with histoplasmin, and 101 were tested with moniliin. Later, in June and July, 1951, an additional 84 patients were tested with both tuberculin and moniliin. There were, then, 537 patients, unselected as to age, sex, race, or diagnosis, tested with tuberculin. Ages varied from premature infants to children 15 years old. The age distribution of children admitted to Children's Hospital is included in the first paper of the series.[1] There were 99 Negroes in the group. Although many persons with hyperpyrexia were given tuberculin, no patient in extremis was tested.

MATERIALS AND PROCEDURE

Materials were handled as described in the preceding paper.[1] Wyeth's old tuberculin was injected intradermally on the volar surface of the right arm. The routine procedure was to introduce 0.1 ml. of 1:10,000 dilution (0.01 mg.). If this dilution produced no reaction, 0.1 ml. of 1:100 dilution (1.0 mg.) was injected. Usually the intermediate dilution (0.1 ml. of 1:1,000, or 0.1 mg.) was omitted because many patients were not hospitalized for so long a period as the eight days required for its inclusion in the procedure. Reactions, including equivocal results, were read and measured at 48 hours.

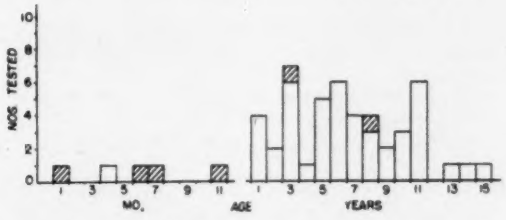
From the Departments of Pathology and Pediatrics, University of Pittsburgh and Children's Hospital.

1. Carpenter, A. M., and Spino, P. D.: Incidence of Skin-Test Reactions Among Children in the Pittsburgh District: I. Histoplasmin, A. M. A. Am. J. Dis. Child., this issue, p. 589.

RESULTS

Of the 537 patients tested with Wyeth's old tuberculin, there were 46 positive and 6 equivocal reactions (9.6%) (Chart). During the winter months, there were 35 true positive and 6 equivocal reactions among 453 persons tested. Of the 89 Negroes tested, 12 (6 boys and 6 girls) had positive reactions (13.4%). Of 364 white patients, 29 (15 boys and 14 girls), or 8.2%, reacted positively. Nine patients with a positive reaction came from rural areas while 32 of them were from urban areas. During the summer period, there were 11 positive reactors, 3 of whom were among the 10 Negro patients. Three of the positive reactors were from a rural area.

Chest roentgenograms were obtained for all but three of the patients who demonstrated tuberculin sensitivity (Table 1). Sixteen roentgenograms showed no abnormalities. Hilar-node enlargement was present in four cases. Increased bronchial markings appeared four times. Frank pulmonary consolidation or infiltration was evidenced in roentgenograms of eight persons. Hilar or parenchymal calcifications were seen in varying degrees in 14 cases; in 5 of these cases the roentgenograms, first reported as normal, revealed small calcifications when reviewed with the knowledge that there was a marked skin-test reaction. Pleural effusion, unilateral, appeared twice, and atelectasis was seen once.



Age distribution of reactors to tuberculin; clear areas represent reactors; hatched areas represent equivocal reactors.

Among the 52 reactors, 10 had a positive reaction to 0.01 mg., as shown in Table 2. Of four additional persons displaying equivocal reactions to this strength, it was possible to continue testing three whose reactions were definitely positive to the 1-mg. concentration. There were nine positive reactions to 0.1 mg.; one further equivocal result at this dilution was positive to the higher concentration. Twenty-one positive reactions were elicited with the 1-mg. skin test; to these may be added the three that had been equivocal at a weaker dilution. There were, as well, five reactions, four among children under one year old, which measured less than 5 mm. after injection of the 1-mg. concentration. The other child under one year old with a bona fide positive reaction to the 1-mg. injection had been studied for azotemia; no focus of tuberculous infection was found.

It is of interest that a study of the histories of these patients (Table 1) revealed that 13 children (25%) had tuberculous contact; 23 (44%) had elevated temperature; 25 (48%) experienced weight loss; 18 (34%) complained of lassitude; 25 (48%) of chronic cough, and 9 (17%) of joint pains. Adenitis was observed in 17 (32%) children.

TABLE 1.—*Pertinent Findings Among the Tuberculin Reactors*

	Race	Age, Yr.	O. T., Mm. 0.01 Mg.	0.1 Mg.	1.0 Mg.	Diagnosis	Roentgenogram	Contact	Fever	Weight Loss	Lassitude	Cough	Joint Pains	Node Enlargement	Sedimentation Rate	Streptomycin	Rural Habitat	
L. H.	W	1 mo.	..	..	2	Multiple anomalies	—	..	+	..	..	..	..	..	..	..	—	.....
G. W.	W	4 mo.	..	..	6	Hypocalcemia	—	—	+	..	+	..	—	..	..	..	—	.....
L. T.	N	6 mo.	..	..	4	Pneumonia	Atelectasis	..	—	..	..	..	..	..	..	..	—	.....
Y. D.	N	7 mo.	3	..	..	Sicklemia	—	..	+	+	+	+	..	—	..	..	..	.....
R. L.	W	11 mo.	..	..	4	Pneumonia	Consolidation	..	..	+	..	+	..	..	9	..	—	.....
A. W.	N	1	5	..	10	Lymphedema	Increased hilar nodes	..	..	+	..	+	..	Liver; +	..	..	—	.....
D. J.	W	1	..	..	20	Miliary T. B.	Infiltration	+1	—	..	..	+	..	—	8	—	+	Necrosis; g. p.—; biopsy-caseus
G. S.	N	1	..	..	6	Diarrhea	Not done	—	+	..	..	+	..	+	..	..	—	.....
J. A. H.	W	1	..	10	..	Cystitis	Increased markings	+3	+	..	..	..	..	+	..	..	—	.....
N. G.	W	2	..	9	..	T. B. meningitis	Consolidation	+1	+	—	+	+	..	—	15	+	—	Died; g. p +; necropsy
D. T.	W	2	8	..	..	T. B. meningitis	Increased hilar nodes	+1	+	..	+	..	..	Liver; +	15	+	+	G. p. +
B. S.	W	3	10	..	..	Feeding problem	—	—	..	+	..	..	..	..	40	..	+	.....
M. M.	W	3	..	..	15	Nephritis	Calcification	—	..	..	..	+	..	—	14	..	—	.....
W. D.	W	3	..	..	9	Coeliac	Pleural effusion	—	+	+	..	+	..	..	10	..	—	.....
G. W.	N	3	..	..	6	Sicklemia	Infiltration	..	+	+	..	+	..	Liver, spleen +	58	..	—	.....
O. T.	N	3	..	..	1	Bronchopneumonia	Consolidation	..	+	..	..	+	..	Liver; +	..	..	—	.....
L. B.	W	3	..	..	5	Nephritis	—	+	+	—	+	+	..	..	44	..	—	.....
M. K.	W	3	..	..	5	Nephritis	—	..	+	—	..	..	..	—	..	..	—	.....
R. J.	W	4	40	..	..	Neoplasm of brain	Calcification	—	—	—	—	+	..	—	15	—	—	.....
W. S.	N	5	22	..	..	Pulmonary T. B.	Pleural effusion	—	+	+	+	+	..	..	25	+	—	G. p. —
H. S.	W	5	24	..	..	Nephritis	—	—	..	+	+	—	..	Liver; +	20	..	—	G. p. —
C. B.	W	5	..	..	7	Arthritis	—	.	..	..	..	..	+	..	15	..	..	.....
J. B.	N	5	..	..	12	Pneumonia	Consilation	+	+	..	..	+	..	+	..	..	—	.....
M. N.	W	5	..	8	..	Undetermined	Not done	—	—	..	..	+	..	..	6	..	+	.....
F. M.	W	6	25	..	..	Primary T. B.	Calcification	—	+	+	..	—	..	..	5	—	—	.....
C. B.	N	6	1	..	7	Rheumatic fever	—	+2	..	+	+	..	+	+	20	..	—	.....
J. G.	W	6	..	22	..	Fever unknown origin	Inc. bilat. markings	..	..	..	+	..	+	..	11	..	—	.....
J. P.	N	6	..	..	12	Convulsions	Calcification	..	..	+	+	..	..	—	12	..	—	.....
A. M.	W	6	..	..	10	Sinusitis	Hilar calcification	..	..	+	..	+	..	+	17	..	—	.....
G. H.	W	6	..	..	6	Encephalitis	Increased markings	+2	+	+	..	+	..	..	..	..	+	.....
F. R.	W	7	..	4	10	Osteomyelitis	Calcification	..	+	..	..	..	+	—	21	..	+	.....
D. M.	W	7	..	..	8	Bronchopneumonia	Infiltration	—	..	..	..	+	..	+	11	..	..	.....
J. W.	N	7	..	..	7	Rheumatic heart	Congestion	—	..	..	—	+	..	Liver; —	..	..	—	.....
C. S.	W	7	..	5	..	Pan-sinusitis	—	..	+	+	+	+	..	..	12	..	+	.....
R. T.	N	8	7	..	..	Dislocated hip	Calcification	+	..	+	..	+	+	..	—	..	—	.....
R. W.	W	8	..	6	..	Poliomyelitis	Increased markings	+	+	+	..	+	..	..	15	..	+	.....
C. S.	W	8	..	..	10	Diabetes	—	..	..	+	..	—	..	..	..	..	+	.....
A. V.	W	8	..	..	5	Pneumonia	Calcification	—	+	+	..	..	..	+	40	..	—	.....
P. N.	W	9	..	10	..	Primary T. B.	Hilar calcification	..	..	+	..	..	+	..	30	..	—	.....
B. R.	W	9	..	..	15	Rheumatic heart	Not done	..	—	—	..	..	..	—	..	..	—	.....
G. A.	N	10	..	25	..	Peptic ulcer	—	—	—	+	—	—	..	..	..	..	—	.....
S. R.	W	10	4	..	17	Primary T. B.	Calcification	—	—	+	..	..	..	+	31	—	+	.....
L. P.	W	10	..	..	7	Heart anomaly	—	..	..	+	+	..	+	—	4	..	+	.....
G. V.	W	11	20	..	..	Vertigo	Calcification	+	..	..	+	..	..	..	14	..	—	.....
E. R.	W	11	23	..	..	Rectal bleeding	Hilar enlargement	—	..	+	+	+	..	—	13	..	—	.....
B. D.	N	11	..	6	..	T. B.	Calcification	—	+	+	+	+	+	—	25	+	—	Died
M. E.	W	11	..	..	41	Sinusitis	—	..	+	—	—	+	+	—	35	..	—	.....
B. R.	W	11	..	..	25	Convulsions	Calcification	—	—	—	+	..	..	—	6	..	—	.....
C. H.	W	11	..	..	6	Vomiting	—	..	—	..	—	—	..	+	..	..	+	.....
B. C.	W	13	..	..	6	Upper respiratory infection	—	..	+	..	+	..	..	+	5	..	—	.....
R. S.	N	14	6	..	..	Osteomyelitis, tuberculous	Calcification	+	..	..	+	..	..	+	16	..	—	Biopsy; skull cyst
T. R.	W	15	..	..	10	Diabetes	Hilar enlargement	+	..	+	..	..	..	..	..	..	—	.....

Supportive laboratory evidence was demonstrated in four cases, two after guinea pig inoculation, two by biopsy. Confirmation of tuberculosis was made at necropsy of one of the two patients who died subsequent to the period of testing.

Sedimentation rates, essential in following the course of patients with active tuberculosis, were not, in this study, correlated with positive reactions because of coincident diseases such as rheumatic fever.

COMMENT

Although the percentage of positive results in this series is high for children, corresponding to that ascribed to adult groups, the data are skewed somewhat because the children were ill. It has been observed [2] that positive reactions to tuberculin are shifting to higher age groups. Whereas previously the peak came in the adolescent years, it has now reportedly advanced to the 25-to-35-year age group.

Acutely ill, febrile, and chronically ill children were tested with little regard to diagnoses. In no case did testing affect the illness.

Equivocal results are only recently attracting attention,[3] possibly as a consequence of mass testing with histoplasmin. It would appear from our data that

TABLE 2.—*Number of Reactions Elicited by the Dilutions of Old Tuberculin*

Strength of O. T., Mg.	Positive Reactions, No.	Equivocal Reactions, No.	
		Positive on Further Testing	Not Tested Further
0.01	10	3	1
0.1	9	1	..
1.0	23	..	5

equivocal reactions are positive. Three patients whose reactions were equivocal to one dilution had positive reactions when tested further; one patient was discharged before additional data could be obtained, and five patients showed an equivocal reaction to the 1-mg. test. Stilwell [4] suggests that testing be continued to 10-mg. concentration. Of the six equivocal reactions, four were in children under one year old.

For nine patients there was a final diagnosis of tuberculosis; of these, five were considered active. Two patients died in the interim between testing and completion of the report. In two cases, one patient admitted with osteomyelitis (R. S.) and one with pleural effusion (W. S.), the tuberculin test was the real guide to diagnosis. Although a child with a positive tuberculin reaction and symptoms of the disease has tuberculosis, to all intents, the physician cannot wait for symptoms of tuberculosis before instituting skin tests.

2. Pascher, F.; Sulzberger, M. B., and Wiener, A. S.: Age Incidence of Positive Tuberculin Reactions (Mantoux), with Statistical Analysis, J. Lab. & Clin. Med. **27**:332, 1941; correction **27**:854, 1942.

3. Palmer, C. E., and Petersen, O. S.: Studies of Pulmonary Findings and Antigen Sensitivity Among Student Nurses: V. Doubtful Reactions to Tuberculin and to Histoplasmin, Pub. Health Rep. **65**:1, 1950.

4. Stilwell, G. G.: Changing Concepts in Tuberculin Testing, M. Clin. North America **32**:1095, 1948.

Routine tuberculin skin tests are not outmoded. Although epidemiologic data indicate a decrease in morbidity, this is no criterion for relaxing the procedure of use in uncovering possible cases of tuberculosis. If investigation is properly instituted, positive tuberculin reactions in preschool children often point to active tuberculous contacts among persons in their immediate environment.

SUMMARY

Results of skin tests with Wyeth's old tuberculin showed 46 positive reactions and 6 equivocal results among 537 patients tested (9.6%). For 15 of 99 Negroes (15.1%) and for 37 of 438 white patients (8.4%) the reactions were positive. Forty of the 52 reactors were from urban areas. There were 28 girls and 22 boys who reacted.

The assistance of Miss Margaret Past, medical record librarian, is acknowledged.

INCIDENCE OF SKIN-TEST REACTIONS AMONG CHILDREN IN THE PITTSBURGH DISTRICT

III. Moniliin

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YEASTS are being isolated from various body foci in increasing numbers of patients admitted to hospitals. The fact is receiving more notice in publications,[1] where it is suggested that the yeast flora, normal inhabitants of the body, overgrow, probably after the destruction of bacterial flora which results from antibiotic therapy. Because no unequivocal or absolute diagnostic aid is available for species of Candida, we considered reevaluating the practicality of using moniliin for skin testing. The major portion of the work [2] referring to the use of this antigen was published before 1939, when, except for the paper of Hill,[3] the antigen was reported of little value in establishing a diagnosis.

SELECTION OF PATIENTS

During a six-week period in January and February, 1951, one hundred infants and children admitted consecutively to the medical services of Children's Hospital were tested with moniliin. Their ages ranged from 8 days to 14 years. There were 16 Negroes, 8 boys and 8 girls. Forty-six boys and 38 girls comprised the group of white patients.

For an equal period during June and July, 1951, a second series of 103 persons was tested. Seven boys and six girls were Negroes. Of the 90 white children, 41 were boys and 49 were girls.

The age distribution of patients tested during the winter and summer periods is shown in the accompanying chart.

From the Departments of Pathology and Pediatrics, University of Pittsburgh and Children's Hospital.

1. Harris, H. J.: Aureomycin and Chloramphenicol in Brucellosis with Special Reference to Side Effects, J. A. M. A. **142**:161 (Jan. 21) 1950. Woods, J. W.; Manning, I. H., and Patterson, C. N.: Monilial Infections Complicating the Therapeutic Use of Antibiotics, ibid. **145**:207, 1951. Merliss, R. R., and Hoffman, A.: Steatorrhea Following the Use of Antibiotics, New England J. Med. **245**:328, 1951.

2. (*a*) Kerr, P. S.; Pascher, F., and Sulzberger, M. B.: Monilia and Trichophyton Extracts: Their Combined Use in Eczematous Ringworm (Dermatophytosis and Dermatophytids), J. Allergy **5**:288, 1934. (*b*) Lewis. G. M.; Hopper, M. E., and Montgomery, R. M.: Infections of Skin Due to M. Albicans: I. Diagnostic Value of Intradermal Testing with a Commercial Extract of Monilia Albicans, New York J. Med. **37**:878, 1937. (*c*) Trussell, R. E.: Hypersensitivity as a Factor in Chronic Monilia Vaginitis, J. Iowa Med. Soc. **29**:485, 1939.

3. Hill, L. W.: Sensitivity to Fungi in Infantile "Eczema," J. A. M. A. **102**:331 (Aug. 4) 1934.

MATERIALS

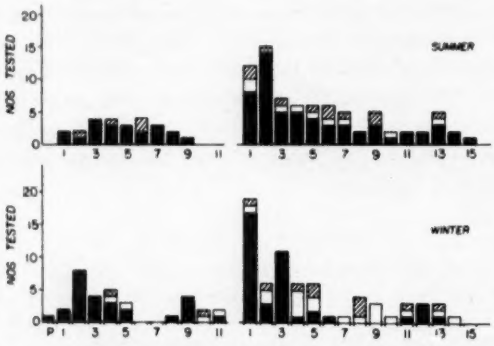
Moniliin ("oidiomycin") was prepared according to the directions of Dr. N. F. Conant[4] of Duke University. A 48-hour culture of Candida albicans, procured from Dr. Conant, was suspended in isotonic sodium chloride solution and was heat-killed for two hours at 56 C. Laboratory personnel were tested with several dilutions of this antigen and with a moniliin prepared by Dr. Conant. Subsequently our material was employed in the dilution which gave reactions comparable in size to that of the reference. At the same time, the biologic standardization was checked with nitrogen determinations using a modified[5] Kjeldahl technique. (In 0.1 ml. of the appropriate dilution for testing skin reactions there is 0.008 mg. of nitrogen.)

PROCEDURES

The technique for skin testing with moniliin and Wyeth's old tuberculin is described in a previous paper.[6] A reaction was termed equivocal when, with induration present, erythema was less than 5 mm. in diameter.

RESULTS

Winter-Testing.—Thirty-four of the one hundred patients tested with moniliin were positive reactors, 24 of 54 boys and 10 of the 46 girls. Of 16 Negroes 4 were positive reactors, 2 boys and 2 girls.



Age distribution of patients tested with moniliin; negative reactors are indicated by solid black areas; positive reactors are indicated by clear areas, and equivocal reactors are indicated by cross hatched areas.

In the test group, 7 persons were both tuberculin-positive and moniliin-positive, 18 were tuberculin-negative but moniliin-positive, and 9 of the tuberculin-negative patients showed equivocal results with moniliin. Of the remaining patients with negative reactions to moniliin, only three were tuberculin-positive. These data are recorded in Table 1.

In Table 2 it is seen that of 32 patients under one year old 6 (18%) were positive reactors to moniliin. In the age group from 1 to 5 years, 10 of 44 patients were positive reactors (25%). From 6 to 10 years, 13 of the 14 persons tested

4. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, W. B. Saunders Company, 1945.

5. Carpenter, A. M.: Dilution of Capillary Blood in the Microanalysis of Protein, Am. J. Clin. Path. **17**:565, 1947.

6. Carpenter, A. M., and Spino, P. D.: Incidence of Skin-Test Reactions Among Children in the Pittsburgh District: I. Histoplasmin, A. M. A. Am. J. Dis. Child, this issue, p. 589.

reacted positively to moniliin, and from 11 to 15 years, 5 of 10 reacted positively. It is interesting that in this series 76% of the children admitted to the medical services were under 5 years old. Twenty-one per cent of the children under 5 years old reacted to moniliin. One patient (E. R.), with a negative reaction to moniliin at 4 months of age, became a reactor at 5 months when erythema was recorded as 11 by 10 mm. in size.

Summer Testing.—Of the 103 patients tested during the summer months 25 had positive reactions to moniliin. Five of thirteen Negroes reacted positively, three boys and two girls. Of 49 white girls, 15 reacted positively, while 10 of the 41 boys displayed positive results.

Five persons were moniliin- and tuberculin-positive; seven had positive reactions to moniliin but negative reactions to tuberculin; two tuberculin-positive children

TABLE 1.—*Distribution of Reactors to the Antigens Used*

	Winter	Summer
Moniliin +, tuberculin +	7	5
Moniliin +, tuberculin −	18	7
Moniliin equivocal, tuberculin +	0	2
Moniliin equivocal, tuberculin −	9	11
Moniliin −, tuberculin +	3	4
Moniliin −, tuberculin −	63	74
	100	103

TABLE 2.—*Age Groups and Type of Reaction Elicited*

	Winter				Summer			
Age, Yr.	No. Tested	Moniliin Positive	Moniliin Equivocal	Tuberculin Positive	No. Tested	Moniliin Positive	Moniliin Equivocal	Tuberculin Positive
Under 1	32	4	2	1	25	0	4	0
1 to 5	44	7	3	4	46	5	5	5
6 to 10	14	8	5	3	20	5	3	4
11 to 15	10	3	2	3	12	2	1	2
Totals	100	22	12	11	103	12	13	11

had equivocal reactions to moniliin, while 11, in whom reaction to moniliin was equivocal, had negative reactions to tuberculin; four reacted positively to tuberculin alone.

Twenty-five children were under one year old; only four were equivocal reactors. Of 46 children in the 1-to-5-year age group, 5 were positive and 5 equivocal reactors. In the group from 6 to 10 years old there were five positive and three equivocal reactions among the 20 persons tested. In the 11-to-15-year group, two positive and one equivocal reactions occurred among the 12 patients.

In this series, 11 of 103 patients reacted positively to old tuberculin. Seven responded positively to both moniliin and tuberculin. There were 71% who were under 5 years old, and 19.7% were positive reactors to moniliin.

Cultures.—Cultures of Candida species were isolated from 14 persons tested with moniliin. Five children from whom cultures were obtained were positive reactors to the antigen, while nine had negative reactions.

During the two winter months, 15 yeasts (1.7%) were isolated from 869 cultures requisitioned in the hospital bacteriology laboratory. Of 3,293 cultures made from January to July, there were 54 recorded as yeast (1.6%). Thus it may be noted that the percentage of these organisms isolated during the periods of testing was remarkably constant. The identification of yeast-like isolates from patients at Children's Hospital is the subject of a subsequent paper.

COMMENT

In an attempt to account for reactors, the histories of the patients were studied; physical findings and laboratory data were charted. The greater number of positive reactors fall into two groups so far as their discharge diagnoses are concerned. To one group may be assigned an allergic background. The other group comprises children with history of repeated infection, usually from birth, with episodes of upper respiratory infection, pharyngitis, tracheobronchitis, laryngitis, and often lymphadenitis. These patients improve, for a time, with one or another regimen with antibiotics. The distribution of positive reactors according to their diagnoses

TABLE 3.—*Discharge Diagnoses of Patients Tested with Moniliin*

Reactions	Winter		Summer	
	Positive	Negative	Positive	Negative
Upper respiratory infections	10	6	2	6
Bronchitis	9	8	1	6
Pneumonia	1	7	2	2
Fever, unknown origin	1	1	1	4
Observation	3	1	1	7
Asthma	2	4	0	0
Rheumatic heart disease	2	7	2	5
Gastrointestinal complaints	1	9	7	10
Hemopoietic disease	0	11	1	12
Nervous disorders	4	9	3	16
Urogenital disorders	0	2	3	7
Congenital defects	1	1	2	3

on discharge is listed in Table 3. It is interesting that the two above-mentioned groups have a comparable number of nonreactors.

Hospital records for 5,750 total admissions during the past year reveal that 2,934 are for medical patients. There were 33% of these medical patients who were under 1 year, and 35% were children from 1 to 5 years old. This total of 78% agrees fairly well with the incidence in our series when it is considered that our group was so small.

Although specificity has been ascribed to moniliin,[2a] our data disclose only that a considerable number of children have been exposed to organisms of the Candida group or to antigenically related species. If serum agglutinins parallel skin-test reactivity, corroborative evidence is given by Norris and Rawson,[7] who demon-

7. Rawson, A. J., and Norris, R. F.: Occurrence of a Common Group Antigen Among Candida Albicans, Saccharomyces Cerevisiae and Hansenula Anomala, Am. J. Clin. Path. **17**:807, 1947. Norris, R. F., and Rawson, A. J.: Occurrence of Serum Agglutinins for Candida Albicans and Saccharomyces Cerevisiae in a Hospital Population, ibid. **17**:813, 1947. Norris, R. F., and Rawson, A. J.: Detection of Serum Agglutinins for Monilia and Other Yeast-like Organisms, Science **105**:105, 1947.

strated common group agglutinins for species of Candida, Saccharomyces, and Willia (Hansenula).

In view of the problematical status of moniliin, it is not apropos to comment on those skin-test results which, by present standards, are equivocal. It would appear that to substantiate employing the antigen as a diagnostic aid, considerable standardizing is necessary, as has been accomplished for histoplasmin by Howell.[8] These findings are not surprising in view of the difficulty of ascribing pathogenicity to members of the genus Candida.

SUMMARY

Of 100 patients on whom skin tests were done during the winter months, 25 reacted positively to moniliin prepared from Candida albicans. Nine displayed equivocal reactions. During the summer months, 12 of 103 patients were positive reactors; 13 were equivocal reactors.

This study contributes no new evidence which would validate employing the antigen, moniliin, as a diagnostic procedure.

8. Howell, A.: Studies of Fungus Antigens: I. Quantitative Studies of Cross Reactions Between Histoplasmin and Blastomycin in Guinea Pigs, Pub. Health Rep. **62**:631, 1947.

ALLERGY TO VIRAL AND RICKETTSIAL VACCINES

II. Allergic Reactions Encountered and Further Studies with Refined Influenza and Mumps Vaccines in Allergic Children

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BECAUSE of the avidity that rickettsiae and viruses have for embryonal tissues, the chick embryo was found to be a desirable culture medium for the preparation of immunizing vaccines. The vaccines which are considered of value as immunizing agents are yellow fever, typhus, Rocky Mountain spotted fever or tick typhus, equine encephalomyelitis, influenza A and B strains of virus, and mumps. However, allergic reactions have resulted as a side-effect from the use of such vaccines in egg-sensitive persons.

Injection of egg protein, as a diagnostic procedure, in exquisitely sensitive children has resulted in profound anaphylactic-shock reactions [1] and death.[2] How frequently one may expect to encounter such persons was estimated by us in previous reports.[3] We found that 20% of 500 allergic children [3c] demonstrated a dermal sensitivity to egg proteins. In only 5% was this sensitivity of clinical significance. We propose in this study to analyze and evaluate the responses to egg-embryo-cultured vaccine injected for immunologic or diagnostic reasons in allergic subjects.

Aided by a grant from the Lederle Laboratories Division, American Cyanamid Company, and the Playtex Park Research Institute.

From the Departments of Pediatrics and Immunology, New York Medical College, Flower and Fifth Avenue Hospitals, and the Pediatric Division, Sea View Hospital.

1. Blackfan, K. D.: A Consideration of Certain Aspects of Protein Hypersensitiveness in Children, Am. J. M. Sc. **160**:341, 1920. Gerstenberger, H. J., and Davis, J. H.: Anaphylaxis Following an Intradermal Protein Sensitization Test, J. A. M. A. **76**:721 (March 12) 1921.

2. Lamson, R. W.: Sudden Death Associated with Injection of Foreign Substances, J. A. M. A. **82**:1091 (April 5) 1924. Baagöe, K. H.: Case of Allergic Death Due to Intracutaneous Injection of 0.1 cc. of White of Hen's Egg, Ugesk. læger **90**:550, 1928.

3. (*a*) Ratner, B., and Untracht, S.: Allergy to Virus and Rickettsial Vaccines: I. Allergy to Influenza A and B Vaccine in Children, J. A. M. A. **132**:899 (Dec. 14) 1946; (*b*) Allergy to Viral and Rickettsial Vaccines: Review of the Literature, Ann. Allergy **8**:699, 1950; (*c*) Egg Allergy in Children: Incidence and Evaluation in Relation to Chick-Embryo-Propagated Vaccines, A. M. A. Am. J. Dis. Child. **83**:309 (March) 1952.

ALLERGIC REACTIVITY TO VIRAL AND RICKETTSIAL VACCINES PREPARED FROM CHICK-EMBRYO CULTURES

A review of reports describing reactions indicates that the entire gamut of allergic reactivity has been witnessed. The types of allergic reactions from viral and rickettsial vaccine injections are classified as follows:

1. Fatal anaphylaxis.[4]
2. Severe anaphylaxis with recovery.[5]
3. Moderate systemic allergic reactions.[6]
4. Serum-sickness-like reactions.[7]
   - A. Systemic reaction, accelerated type.[7]
   - B. Local reaction, accelerated type.[8]
   - C. Typical serum-sickness-like reaction.[7]
   - D. Local serum-sickness-like reaction.[8b]
5. Immediate dermal reactions (noted in above reports).
6. Local delayed dermal reactions.[9]

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(Footnote continued on next page)

Three deaths were reported following the subcutaneous injection of typhus vaccine,[10] two from influenza vaccine,[11] and one after spotted fever vaccine.[4c] In three instances, a typical guinea-pig type of anaphylaxis was noted at autopsy.[10] Each of these patients was highly sensitive to egg clinically. In Curphey's case,[4d] a marked bleeding tendency, which started four hours after injection, developed in the child shortly before death. There was no history of egg intolerance in the last instance.

A case [3a] of vascular collapse (canine type of anaphylaxis) without respiratory symptoms, following influenza-virus vaccine, is interesting. The patient had a clinical aversion to egg.

There are three instances of a generalized reaction following an intracutaneous test dose, two with typhus [6c] and one with influenza vaccine.[3a] In each, further therapeutic injection was withheld. It is of interest that in Raynold's case [6c] no local reaction was observed.

Fig. 1.—Results of intradermal injection of 0.02 cc. each of (*1*) egg white 1:500; (*2*) formalin 1:2,000, thimerosal (merthiolate®) 1:40,000; (*3*) isotonic sodium chloride; (*4*) red-blood-cell-eluate influenza vaccine undiluted; (*5*) Sharples influenza vaccine undiluted; (*6*) alcohol-precipitated influenza vaccine undiluted.

Serum-sickness-like reactions,[7] generalized in two instances, followed six and seven days, respectively, after yellow-fever vaccine. In another reported case the same symptom complex developed after 36 hours, suggesting an accelerated serum-sickness-like picture. Stull [8b] described a reaction of the local serum-

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10. Rifkin.[4a] Walker.[4b] Plotz.[4c]
11. Plotz.[4c] Curphey.[4d]

sickness type after equine-encephalomyelitis vaccine. The recipient revealed local erythema and induration plus urticaria seven days after the first injection, but the same type of local reaction developed within one hour after the second injection given two weeks later.

Local allergic reactions of the immediate type, in the form of erythema surrounding a central wheal with pseudopodia, have been noted in egg-sensitive persons following test intradermal injections of vaccine. Apart from this immediate reaction, due to egg protein, the test dose may elicit a delayed reaction at the site of the injection.[12] There is evidence for the belief that this delayed reaction is allergic in nature and reflects previous experience with the virus. Chick-embryo-propagated virus vaccines have been demonstrated to retain this ability to elicit virus protein sensitivity. The viruses of venereal lymphogranuloma, influenza, mumps, and herpes simplex have been utilized in this manner to diagnose previous experience with these infections.

Fig. 2.—Results of intradermal injection of 0.1 cc. each of (*1*) mumps vaccine, (*2*) red-blood-cell-eluate influenza vaccine, and (*3*) isotonic sodium chloride solution.

COMPARATIVE DERMAL ALLERGIC REACTIONS FOLLOWING TEST DOSES OF INFLUENZA-VIRUS VACCINES AND MUMPS VACCINE

Dermal Reaction to Influenza-Virus Vaccine.—The comparative antigenicity, with regard to egg protein, of the three types of influenza-virus vaccines was studied. The following types of influenza-A- and B-virus vaccines were employed:

1. Red blood cell eluate vaccine, a virus concentrated by adsorption on and elution from red blood corpuscles of the chick embryo.[13]

2. Sharples centrifuged-type vaccine, a concentration of the virus by differential ultracentrifugation.[14]

3. Alcohol-precipitated vaccine, a concentration of virus by precipitation with methanol and separation by ultracentrifugation.[15]

12. Footnote 8*c* and *d*. Footnote 9.

13. Francis, T., Jr., and Salk, J. E.: A Simplified Procedure for the Concentration and Purification of Influenza Virus, Science **96**:499, 1942.

14. Stanley, W. M.: The Preparation and Properties of Influenza Virus Vaccines Concentrated and Purified by Differential Centrifugation, J. Exper. Med. **81**:193, 1945.

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Table 1 presents the data on 140 children. It will be noted that more marked reactions were elicited with the red-blood-cell-eluate type than with the Sharples and alcohol-precipitated influenza vaccines or the mumps vaccine (Sharples centrifuged). This is due to the fact that the last three types of vaccine contain less chick-embryo protein than does the red-blood-cell-eluate type.

TABLE 1.—*Comparative Dermal Hypersensitivity Reactions to Influenza Virus Vaccines, Egg Proteins and Formalin-Thimerosal (Merthiolate®) in a Random Selection of 140 Children*

	Influenza Virus Vaccines			Egg Proteins		Formalin, 1:2,000; Merthiolate, 1:40,000
Case	RBC Eluate	Sharples Centrifuged	Alcohol Precipitated	Egg White	Egg Yolk	
K. K.	+++	++	+	+++	+	0
J. D.	++	+	+	+	0	0
L. W.	+++	+	+	+	+	0
H. M.	+	+	+	0	0	+
R. W.	+	+	±	0	0	+
S. B.	+	+	+	0	0	+
E. F.	++	++	++	0	0	++
E. G.	+	+	+	0	0	++
C. W.	+	+	+	0	0	++
131 Remaining Cases	0	0	0	0	0	0

TABLE 2.—*Dermal Hypersensitivity to Chick-Embryo-Propagated Mumps Vaccine Following Test Dose in Egg-Sensitive Children*

Patient	Dermal Reaction Following Intradermal Test Dose of Mumps Vaccine*	Evaluation of Clinical Sensitivity to Egg Proteins
M. H.	+++	Highly sensitive
R. S.	+++	
M. K.	++	Moderately sensitive
S. S.	++	
S. T.	++	
A. W.	++	
B. F.	++	
K. K.	++	
H. S.	++	
B. W.	++	Clinically immune at present but highly sensitive in the past; residual dermal sensitivity persists
M. G.	++	
K. H.	+	
E. P.	+	
A. S.	+	
H. A.	+	
A. S.	0	Clinically immune; positive egg-white dermal reactions in the past, but no clinical sensitivity to egg ever established
V. D.	0	
S. G.	0	
R. P.	0	

* Dermal reactions, read 15 minutes following intradermal injection, were graded as follows:
+++ Wheal 2.5 cm. or over, erythema 3.5 cm. or over.
++ Wheal 1.0 to 2.0 cm., erythema not over 3.5 cm.
+ Wheal 0.5 to 1.0 cm., erythema not over 2.5 cm.
0 No reaction greater than sodium chloride control injection.

It was observed that those patients who were sensitive to formalin reacted equally to each of the three types of vaccine. In the same table are listed six children, who did not react to egg but who did react to the virus vaccine and the formalin. The vaccine reactivity is therefore, in all probability, due to the formalin content. In the remaining 131 cases the children failed to react and served as a control series.

Dermal Reaction to Mumps Vaccine.—Nineteen egg-sensitive children were tested with mumps vaccine (Table 2). A test dose of 0.05 cc. (1:5 dilution of

virus) was injected intradermally. No untoward reactions ensued from the test dose. The immediate response in these egg-sensitive children was essentially the same as that noted with the Sharples centrifuged influenza vaccine (Table 1).

ALLERGIC REACTIONS TO PROPHYLACTIC INJECTIONS OF INFLUENZA VIRUS VACCINES IN EGG-SENSITIVE CHILDREN

It was evident from the review of the experiences with these vaccines in allergic subjects that there is need for further study of the effects of prophylactic injections and, more particularly, with the test dose of the vaccine. An analysis of allergic responses from prophylactic vaccine injections in egg-sensitive children follows:

A. Red-Blood-Cell-Eluate Vaccine.—Experiment I: An intradermal injection of diagnostic test dose (0.02 cc.) of red-blood-cell-eluate undiluted vaccine was administered to an exquisitely sensitive child. This child, L. D., aged 9 years, was known to be decidedly sensitive to egg, ingestion of which had caused gastrointestinal disturbances and asthma since infancy. A

TABLE 3.—*Allergic Systemic Reactions Following Test and Prophylactic Injections of Chick-Embryo-Propagated Influenza-Virus Vaccine in Children Exquisitely Sensitive to Egg Protein*

		Reactions to R. B. C. Eluate Type of Influenza-Virus Vaccine	
Case	Degree of Clinical Sensitivity to Egg Proteins	Dermal Reaction to Test, Dose 0.02 Cc.	Systemic Allergic Response to Test and/or Prophylactic Injection
L. D.	Exquisite	++++*	No prophylactic injection was given in view of the systemic anaphylactic reaction which followed the test dose. An attack of asthma developed which persisted for about 12 hr. despite injections of epinephrine.
P. L.	Exquisite	++++	Injection of 0.5 cc. undiluted vaccine was followed in 20 min. by generalized urticaria and angioneurotic edema with severe itching, especially at injection site

* ++++ Wheal over 3.5 cm., erythema over 5 cm. within 15 minutes after injection.

generalized reaction developed from the test dose (Table 3). The occurrence of such a systemic reaction to an intracutaneous injection is an absolute contraindication to further injection.

Experiment II: Subcutaneous injections of undiluted crude red-blood-cell-eluate vaccine were given to children moderately to highly egg-sensitive. P. L. was clinically sensitive to egg. Since he exhibited a large local response to the test dose without a systemic reaction, his sensitivity was challenged with a prophylactic dose of 0.05 cc. subcutaneously. Within 10 minutes a generalized reaction developed (Table 3). No further tests were done because of the systemic reaction encountered.

Three additional children (Table 4) tolerated the prophylactic dose with no ill effect. Of these three, only K. K. was clinically egg-sensitive to a moderate degree. The remaining two, aged 14 and 16 years respectively, represent persons immune to egg, although they were known to have been sensitive in the past. They both demonstrate residual dermal sensitivity.[8e]

Experiment III: Subcutaneous injections of red-blood-cell-eluate vaccine diluted 1:10 were used for children with moderate to minimal egg sensitivity (Table 5). We felt from the above experiences that the use of the cruder vaccine (red-blood-cell-eluate) may still be hazardous if not further diluted. We, therefore, diluted the vaccine 10 times with buffered isotonic sodium chloride solution and then proceeded to test the next group of egg-sensitive children with smaller doses, subcutaneously, and took the precaution of simultaneously injecting a small dose (2 minims [0.12 cc.]) of 1:1000 epinephrine hydrochloride solution freshly drawn into the same syringe. Seven children were given from 2 to 20 injections of 0.15 cc. of the diluted vaccine. Injections were administered at intervals of one week. All tolerated these doses with no untoward effects.

Only one of this group (B. F.) was considered clinically sensitive to egg. This child has eczema and asthma. The remaining are clinically immune to egg, but retain residual dermal sensitivity.

Experiment IV: Prophylactic intradermal injections of red-blood-cell-eluate undiluted vaccine were administered to clinically immune and dermally egg-sensitive children (Table 6).[7]

TABLE 4.—*Allergic Reactions Following Test and Prophylactic Injections of Chick-Embryo-Propagated Influenza-Virus Vaccine in Moderately and Clinically Immune Egg-Sensitive Children*

		Reactions to R. B. C. Eluate Type of Influenza-Virus Vaccine		
		Dermal Reaction to Intradermal Test Dose, 0.02 Cc.	Subcutaneous Prophylactic Dose, 0.5 Cc. Undiluted†	
Case	Degree of Clinical Sensitivity to Egg Proteins		Local Reaction at Injection Site	Systemic Reaction
K. K.	Moderate	+++	Itching and moderate edema	None
B. W.	Now clinically immune; formerly highly sensitive	++	Itching	None
T. H.	Immune	±	None (2)‡	None

* Dermal reactions were evaluated as follows:
+++ Wheal 2.5 cm., erythema 4.0 cm.
++ Wheal 2.0 cm., erythema 3.0 cm.
+ Wheal 1.0 cm., erythema 2.0 cm.
± Reaction little larger than sodium chloride control.

† Injection given with 2 minims epinephrine drawn into same syringe as a safety factor in view of the systemic reactions noted in Table 3.

‡ Number in parentheses refers to total number of injections given.

TABLE 5.—*Allergic Reactions Following Test and Repeated Prophylactic Injections of Chick-Embryo-Propagated Influenza-Virus Vaccine in Moderate and Immune Egg-Sensitive Children*

		Reactions to R. B. C. Eluate Type of Influenza-Virus Vaccine		
		Dermal Reaction to Intradermal Test Dose, 0.02 Cc.	Subcutaneous Prophylactic Dose, 0.15 Cc. Diluted 1:10 Given at Weekly Intervals*	
Case	Degree of Clinical Sensitivity to Egg Proteins		Local Reaction at Injection Site	Systemic Reaction
B. F.	Moderate	++	None (3)†	None
B. H.	Now immune; was highly sensitive	++	Itching (5)	None
B. W.	Now immune; was highly sensitive	++	Edema (6)	None
E. H.	Now immune; was moderately sensitive	++	None (2)	None
E. P.	Now immune; was exquisitely sensitive	+	None (2)	None
M. F.	Immune	+	None (8)	None
R. P.	Immune	+	None (20)	None

* Each injection was given with 2 minims epinephrine drawn into same syringe.

† Number in parentheses refers to total number of injections given.

We injected by the intradermal route instead of the subcutaneous, since it was shown that the intradermal route provided antibody titer levels which may be adequate for protection.[16] In this fashion eight children were given injections. Large local reactions followed the first 15-minute period, with erythema (4 to 6 cm.) and wheals (2 to 2.5 cm.) with pseudopodia. No generalized reaction ensued. The local reaction resolved in the next 24-to-28-hour period. This suggests that the intradermal route may safely be used if the patients are not exquisitely sensitive.

16. The titrations were done under the direction of Dr. Floyd S. Markham, of the Section for Viral and Rickettsial Research, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

Refined Influenza Vaccine (Sharples Centrifuged Type).—Experiment I: Intradermal injection of Sharples centrifuged vaccine were used in moderately to highly egg-sensitive children. In the highly sensitive group (Table 7) (M. H., E. D., and D. D.) a large local response appeared after 15 minutes, with no systemic reaction. That no reaction ensued after the

TABLE 6.—*Allergic Reactions Following Test and Prophylactic Injections of Chick-Embryo-Propagated Influenza-Virus Vaccine in Moderate to Immune Egg-Sensitive Children*

		Reactions to R. B. C. Eluate Type of Influenza-Virus Vaccine		
		Dermal Reaction to Intradermal Test Dose, 0.02 Cc.	Intradermal Prophylactic Injection, 0.1 Cc. Given 4 Wk. Apart	
Case	Degree of Clinical Sensitivity to Egg Proteins		Local Reaction at Injection Site	Systemic Reaction
D. D.	Definite	+++	Moderate local wheal with itching	None
K. K.	Moderate	++	Moderate local wheal with itching (2)*	None
F. C.	Moderate	++	Moderate local wheal with itching (2)	None
T. C.	Moderate	++	Moderate local wheal with itching (1)	None
M. G.	Immune	++	Wheal (1)	None
J. D.	Immune	++	Wheal (2)	None
T. P.	Immune	+	None (1)	None
R. P.	Immune	+	None (2)	None

* Number refers to injections given.

TABLE 7.—*Allergic Reactions Following Test and Prophylactic Injections of Chick-Embryo-Propagated Influenza-Virus Vaccine in Egg-Sensitive Children*

		Reactions to Sharples Type of Influenza-Virus Vaccine		
		Dermal Reaction to Test Dose, 0.02 Cc.	Intradermal Prophylactic Injection, 0.1 Cc. Given at Intervals of 1 Wk.	
Case	Degree of Clinical Sensitivity to Egg Proteins		Local Reaction at Injection Site	Systemic Reaction
M. H.	High	+++	Moderate edema (2)	None
E. D.	High	+++	Moderate edema (1)	None
D. D.	High	+++	Moderate edema (1)	None
K. K.	Moderate	+++	Moderate edema (3)	None
F. C.	Moderate	++	Moderate edema (8)	None
T. C.	Moderate	++	Moderate edema (7)	None
B. F.	Moderate	++	Little edema (2)	None
L. W.	Immune	++	Little edema (2)	None
B. W.	Immune	++	Little edema (3)	None
E. P.	Immune	+	None (2)	None
M. F.	Immune	+	None (2)	None
M. K.	Immune	+	None (1)	None
V. D.	Immune	+	None (3)	None
M. F.	Immune	+	None (2)	None

prophylactic intradermal injection is especially interesting in M. H., aged 17 years. She had suffered a generalized reaction, with asthma and urticaria, when tested clinically by ingestion of egg. After only 5 drops of raw egg white, well diluted in water, had been swallowed, her lips and tongue swelled, and cramps, nausea, and vomiting developed. Within the next four hours, wheezing, with generalized erythema and urticaria, and partial collapse ensued. Eight recipients of her serum, by passive transfer, had positive reactions to egg white.

The moderately sensitive group received from two to eight intradermal injections with no ill effects. In the patients with residual dermal sensitivity and no clinical intolerance, 17 such injections were given with no untoward sequelae (Table 7).

Thus by 14 children with moderate to high degrees of egg sensitivity, a total of 39 intradermal injections of a purified influenza-virus vaccine, relatively protein-poor, was well tolerated.

Experiment II: Subcutaneous injection of Sharples centrifuged vaccine was used in moderate to immune sensitive children.

Encouraged by the absence of generalized allergic reactions to the intradermal injection of the Sharples centrifuged vaccine, we proceeded to procure additional data on the effect of its subcutaneous injection (Table 8). It should be recalled that, using the subcutaneous route, we had previously noted one systemic reaction (Table 3, P. L.) to the relatively impure red-blood-cell-eluate vaccine. This experience provided a sharp contrast with the results when we employed the more refined Sharples centrifuged vaccine, with which no untoward effects were noted.

TABLE 8.—*Allergic Reactions Following Test and Prophylactic Injections of Chick-Embryo-Propagated Influenza-Virus Vaccine in Children Sensitive to Egg Protein*

		Reactions to Test and Prophylactic Injections of Sharples Type Influenza-Virus Vaccine		
			Subcutaneous Prophylactic Injection, 0.15 Cc.	
Case	Degree of Clinical Sensitivity to Egg Proteins	Dermal Reaction to Test Dose, 0.02 Cc.	Local Reaction at Injection Site	Systemic Reaction
K. K.	Moderate	+++	None (2)	None
B. F.	Moderate	++	None (2)	None
S. T.	Moderate	++	None (2)	None
S. G.	Moderate	++	None (1)	None
H. S.	Moderate	++	None (1)	None
B. W.	Immune; formerly highly sensitive	++	None (4)	None
E. H.	Immune; formerly highly sensitive	++	None (1)	None
M. G.	Immune	+	None (2)	None
B. A.	Immune	+	None (4)	None
M. F.	Immune	+	None (2)	None
T. H.	Immune	±	None (4)	None
M. K.	Immune	+	None (1)	None
B. R.	Immune	+	None (2)	None
A. S.	Immune	+	None (2)	None
M. S.	Immune	+	None (1)	None

INFLUENZA AND MUMPS VACCINE IN ALLERGIC CHILDREN NOT SENSITIVE TO EGG PROTEINS

During the course of these studies, influenza-A and B virus vaccines were given prophylactically to 248 allergic children who were shown to be not sensitive to egg, and in not a single instance was any allergic reaction to the vaccine noted.

The diagnostic test for susceptibility or immunity to mumps was repeatedly performed on 93 allergic patients, not sensitive to egg. In no instance was there any untoward reaction with a mumps vaccine so employed.

SUMMARY AND CONCLUSIONS

Because egg proteins are found in viral and rickettsial vaccines, the use of such vaccines in egg-sensitive persons may result in allergic episodes, encompassing the entire gamut of allergic reactivity.

A direct relation was found between allergenicity and the chick-embryo-protein content of the vaccines. Thus red-blood-cell-eluate vaccines containing the greatest amount of egg proteins elicited greater reactions than the Sharples centrifuged or alcohol-precipitated vaccines, the latter perhaps being the least allergenic.

The criteria for determining the allergic hazard prior to therapeutic use of a vaccine are evaluated as follows:

(*a*) An intradermal injection of 0.02 cc. of the vaccine is of prime value in determining the degree of sensitivity.

(*b*) If a systemic reaction ensues, it is evidence of a high degree of sensitivity. The vaccine should then be withheld or given in small diluted and fractionated doses, perferably intradermally, in conjunction with several minims of epinephrine.

(*c*) If only a large local reaction ensues with the test dose, the vaccine can be diluted and administered with 2 minims of epinephrine.

(*d*) A history of sensitivity to egg, while valuable, is not as reliable a criterion as the intradermal test with the vaccine itself.

With purified influenza vaccine, poor in egg-protein, it was determined that 0.1 to 0.15 cc. may safely be given intradermally or subcutaneously, with the added precaution of 2 minims of epinephrine, to moderately or even highly egg-sensitive subjects.

With mumps-virus vaccine which is also reduced in egg-protein content, the test dose of 0.05 cc. intradermally was well tolerated by egg-sensitive subjects.

No reactions were noted in several hundred non-egg-sensitive allergic children repeatedly given injections of influenza and mumps vaccine.

Reactions in certain non-egg-sensitive children were shown to be due to the formalin incorporated in the vaccine.

We believe that the allergic hazards and unnecessary deaths which have resulted from the use of viral and rickettsial vaccines can be eliminated (*a*) by the reduction of egg-protein content in such vaccines, (*b*) if due regard is given to the criteria herein set forth for determining sensitivity prior to the administration of such vaccines, and (*c*) if due caution is exercised in the use of these vaccines in egg-sensitive subjects.

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Dr. Perry Cohen, former Resident at Sea View Hospital, gave technical assistance in part of this study.

WATER METABOLISM IN WATER INTOXICATION

Review of Basic Concepts

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HISTORY

IN HIS classic study of the effects on mammals of the administration of excessive quantities of water, Rowntree [1] stated that physiologists were apparently the first to notice the toxicity of fresh water for lower orders of life. In 1866 Bert [2] ascribed the toxic effect of fresh water for the mullet to the difference in osmotic pressure between fresh water and sea water, the former causing the tissues to absorb water in excess. In 1904 Bullot [3] proved the toxicity of distilled water for the fresh-water grammarus and also found that the addition of sodium chloride, sufficient to yield 0.000008-molar salt solution, was effective in overcoming the toxicity. In 1921 Miller and Williams [4] studied the effect of excessive intake of water, clinically, on the blood pressure and nonprotein nitrogen in the blood of three patients with renal disease who were given 5 to 15 liters of water orally per day. Two of the patients became dizzy and restless, and complained of headache, and one of the two had vomiting, as well as cramps in the legs.

In 1922 Weir, Larson, and Rowntree [5] reported on three patients with diabetes insipidus who continued their usual intake of 8 to 10 liters of water daily after receiving pituitary extract subcutaneously. Within a few hours these patients complained of headache, nausea, asthenia, incoordination, and staggering gait, and in one instance slight edema appeared. Because the reactions were extremely severe and in one case alarming, the investigators carried out animal studies by giving dogs 50 cc. of water per kilogram of body weight every hour by stomach tube after the administration of pituitary extract subcutaneously. Later dogs, cats, rabbits, guinea pigs, and rats were given double this amount, or 50 cc. of water per kilogram every 30 minutes, and no pituitary extract was given. The reaction was essentially the

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same in the two groups. In four to six hours there developed "restlessness, asthenia, polyuria, diarrhea, salivation, frothing at the mouth, nausea, retching, vomiting, tremor and twitching of muscles, ataxia, tonic and clonic convulsions, collapse, stupor and coma, and, at times, oliguria with progression to death." This reaction to excess of water, Weir, Larson, and Rowntree called "water intoxication."

EXPERIMENTAL INVESTIGATIONS

From these original studies and later ones Rowntree and his co-workers [6] reported the following findings. 1. Excretion of urinary chlorides could be minimal at the time of development of symptoms. 2. The carbon dioxide combining power of plasma in eight experimental animals was either normal or below normal, and the mean averaged 6 vol. % lower than the control mean. 3. The values for serum sodium, chloride, and potassium were reduced more than would be anticipated from the degree of blood dilution. 4. Dilution of the blood was evidenced by relative decrease in hemoglobin, serum proteins, viscosity, electric conduction, and molecular concentration, with corresponding increase in plasma volume. 5. There was a fall in body temperature of the animals which was marked when the water was cold and slight when the water was 50 C. 6. The rise in intracranial pressure, which accompanied and probably caused the symptoms, probably resulted from disturbance in the "salt to water equilibrium of the body and of the central nervous system." They noted the beneficial effect of intravenous administration of hypertonic sodium chloride solution and concluded that water intoxication could be prevented, alleviated, or cured by timely intravenous administration of this solution.

Other investigators studied various phases of this new entity and in general confirmed the findings of Weir and his co-workers,[5] although there was disagreement on some points. Underhill and Sallick [7] found that in 24-hour periods during which water intoxication was induced total urinary chlorides were increased because of the tremendous increase in urinary volume, when compared with control periods. Though the concentration of urinary chloride was diminished, the marked increase in volume of urine accounted for the increased total output of chloride. Davis [8] said that the correlation of the changes in oxygen content of the blood, the rate of oxygen consumption, and the dilution of hemoglobin during the administration of excessive amounts of fluid indicated that the symptoms of water intoxication were those, in part, of an anoxemia. He used both isotonic sodium chloride solution and 5% solution of glucose intravenously, but did find that symptoms "occurred more readily" with glucose solution. Lack of detail in his report made evaluation of symptoms resulting from excessive amounts of isotonic sodium chloride solution difficult. Smyth, Deamer, and Phatak [9] concluded from experimental studies that neither retention of water in their experimental dogs nor hemodilution was the most

6. Rowntree.[1] Weir, Larson, and Rowntree.[5] Greene, C. H., and Rowntree, L. G.: The Effect of the Experimental Administration of Excessive Amounts of Water: I. On the Volume and Concentration of the Blood, Am. J. Physiol. **80**:209-229 (March) 1927.

7. Underhill, F. P., and Sallick, M. A.: On the Mechanism of Water Intoxication, J. Biol. Chem. **63**:61-69 (Feb.) 1925.

8. Davis, H. A.: Studies in Water Balance: Anoxemia Factor in Water Intoxication, Proc. Soc. Exper. Biol. & Med. **33**:245-246 (Nov.) 1935.

9. Smyth, F. S.; Deamer, W. C., and Phatak, N. M.: Studies in So-Called Water Intoxication, J. Clin. Invest. **12**:55-65 (Jan.) 1933.

essential feature of "so-called water intoxication." They expressed the belief that the convulsive symptoms were more closely associated with loss of chloride by way of gastric secretion than with retention of water, whether the loss occurred as a result of vomiting or as a result of gastric dilatation with pooling of electrolytes and a resulting alkalosis. Smyth and his co-workers [9] also noted the absence of benefit from the use of urea in attempting to control symptoms, as had Harding and Harris [10] earlier.

Helwig, Schutz, and Curry,[11] in experimental studies on rabbits, produced water intoxication with water administered by proctoclysis. They found increased chloride content in the liver and stated that Nisawa had recorded this fact experimentally in 1926. The rabbits did not vomit, but at necropsy the stomachs were greatly dilated. The carbon dioxide combining power, determined in only two animals, was reduced in both. Ferraro [12] documented the histologic changes in brain tissue of rabbits resulting from intravenous injection of distilled water. He found that the neurones showed vacuolization of the cytoplasm, swelling of the nucleus, and eventually complete liquefaction, while the axones were involved principally by diffuse swelling of the myelin component. The neuroglia showed acute swelling, and some underwent clasmatodendrosis or acute degenerative changes. The perivascular and perineuronal spaces were markedly dilated, with some predilection for the internal layers of the cortex in general and of Ammon's horn in particular. The choroid plexuses appeared vacuolated, while the ependymal lining cells of the ventricles were generally shrunken. The small blood vessels reacted in the most severe circumstances by a pronounced swelling of the lining epithelium of the intima. Keith [13] found that large amounts of water administered to rabbits by stomach tube increased the fluid content of the brain and the susceptibility to convulsions induced experimentally by thujone. Significantly, he noted that a maximal increase in the fluid content of the rabbit's brain, as measured by change in weight and produced by the intravenous administration of hypotonic sodium chloride solution (0.45%), did not increase susceptibility to thujone convulsions.

Gellhorn and Ballin [14] studied the electroencephalographic changes accompanying water intoxication in rats. They found that slow waves of frequency of one to three per second and amplitude of 100 to 300 μv. appeared singly or in groups to an increasing degree with progressive water intoxication. They also suggested that the changes observed in petit mal, grand mal, and psychomotor seizures could result from the same basic disturbances in function of the brain, since similar changes in the electroencephalogram could be induced by the clearly defined experimental con-

10. Harding, V. J., and Harris, L. J.: Urea Administration in Water Intoxication, Tr. Roy. Soc., Canada (Sect. V, Biol. Sc.) **24**:101-110 (May) 1930.

11. Helwig, F. C.; Schutz, C. B., and Curry, D. E.: Water Intoxication: Report of a Fatal Human Case, with Clinical, Pathologic and Experimental Studies, J. A. M. A. **104**:1569-1575 (May 4) 1935.

12. Ferraro, A.: The Reaction of the Brain Tissue to Intravenous Injection of Hypotonic Solutions, J. Nerv. & Ment. Dis. **71**:129-144 (Feb.) 1930.

13. Keith, H. M.: Experimentally Produced Convulsions: Effect on Thujone Convulsions of Insulin and of Variations in Water Content of Brain, Arch. Neurol. & Psychiat. **33**:353-359 (Feb.) 1935.

14. Gellhorn, E., and Ballin, H. M.: Water Intoxication and Electroencephalogram, Am. J. Physiol. **146**:559-566 (July) 1946.

dition of water intoxication. Cohn, Kolb, and Mulder [15] studied electroencephalographic changes during water-betahypophamine tests on 23 patients. They found low-frequency activity in nearly all patients and concluded that similar bioelectric changes in insulin-induced hypoglycemia, oxygen poisoning, and betahypophamine-hydration tests indicated that all three are probably phenomena of intraneuronal dysfunction.

KNOWN FACTORS INFLUENCING WATER INTOXICATION

Adrenocortical Hormones.—It is now well known that humans and animals with adrenocortical insufficiency show increased susceptibility to water intoxication. Rowntree and Snell [16] in 1931 reported delayed diuresis in patients with adrenal cortex hypofunction (Addison's disease). This was confirmed experimentally on adrenalectomized animals in 1933 by Silvette and Britton,[17] who expressed the belief that increased tissue avidity for water explained this phenomenon. According to Gaunt,[18] Rigler, in 1935, found delayed diuresis and increased susceptibility to water intoxication in adrenalectomized mice given fluid either intraperitoneally or by mouth. Swingle and his co-workers [19] confirmed this experimentally in dogs in 1937, and in 1941 they [20] reported that priming doses of desoxycorticosterone acetate protected adrenalectomized dogs against water intoxication. Eversole, Gaunt, and Kendall [21] in 1942 confirmed the effectiveness of desoxycorticosterone acetate in preventing water intoxication following adrenalectomy but found cortical extract, cortisone, more effective.

Gaunt, who with his co-workers has contributed much to determining the role of the adrenal cortex in water metabolism, with Birnie and Eversole [22] in 1949 concluded that there were the following modes of action of adrenal cortex hormones in water metabolism. 1. There was direct action on renal mechanisms to stimulate the rate and extent of water excretion independent of electrolyte metabolism. This was effected primarily by inhibition of renal tubular reabsorption of water, an action which was antagonistic to that of the antidiuretic hormones. Maintenance of normal glomerular filtration rate by the hormones was also important. 2. There was retention of sodium and chloride ions by stimulation of selective tubular reabsorption. 3. Vague extrarenal effects have been demonstrated experimentally

15. Cohn, R.; Kolb, L. C., and Mulder, D. W.: Electroencephalographic Changes Induced by Water Intoxication, J. Nerv. & Ment. Dis. **106**:513-526 (Nov.) 1947.

16. Rowntree, L. G., and Snell, A. M.: A Clinical Study of Addison's Disease, Philadelphia, W. B. Saunders Company, 1931, p. 195.

17. Silvette, H., and Britton, S. W.: Effects of Adrenalectomy and Cortico-Adrenal Extract on Renal Excretion and Tissue Fluids, Am. J. Physiol. **104**:399-411 (May) 1933.

18. Gaunt, R.: Water Diuresis and Water Intoxication in Relation to Adrenal Cortex, Endocrinology **34**:400-415 (June) 1944.

19. Swingle, W. W.; Parkins, W. M.; Taylor, A. R., and Hays, H. W.: A Study of Water Intoxication in the Intact and Adrenalectomized Dog and the Influence of Adrenal Cortical Hormone upon Fluid and Electrolyte Distribution, Am. J. Physiol. **119**:557-566 (July) 1937.

20. Swingle, W. W.; Remington, J. W.; Hays, H. W., and Collings, W. D.: Effectiveness of Priming Doses of Desoxycorticosterone Acetate in Protecting Adrenalectomized Dogs Against Water Intoxication, Endocrinology **28**:531-534 (April) 1941.

21. Eversole, W. J.; Gaunt, R., and Kendall, E. C.: The Effect of Adrenal Steroids in Water Intoxication, Am. J. Physiol. **135**:378-382 (Jan.) 1942.

22. Gaunt, R.; Birnie, J. H., and Eversole, W. J.: Adrenal Cortex and Water Metabolism, Physiol. Rev. **29**:281-310 (Oct.) 1949.

when the adrenal cortex hormone represented the difference between life and death at the time that excessive water was given adrenalectomized animals which had also had bilateral nephrectomy. The protective factor was postulated to result from altered internal distribution of fluid. 4. There was reduction in the absorption of water from the intestine, which was considered unimportant.

Antidiuretic Hormone of the Neurohypophysis.—Increased susceptibility to water intoxication in adrenocortical insufficiency may also result from the unopposed action of the antidiuretic hormone of the neurohypophysis. Gaunt and his co-workers noted that the antidiuretic hormone of the neurohypophysis increased the renal tubular reabsorption of water and inhibited tubular reabsorption of sodium and chloride ions and that these actions were opposed by the adrenal cortex hormones. One of the facts against a coordinate inverse relation between antidiuretic and adrenal cortex hormones is that the antidiuretic hormone is secreted at varying rates in direct response to changing osmotic pressure in the plasma resulting from variable states of hydration and electrolyte concentration. Present knowledge does not relate the production or release of adrenal cortex hormone to changes in the osmotic pressure of plasma. An increased output of antidiuretic hormone might effectively antagonize the adrenal cortex hormones in its effect on water balance within fairly wide limits; but when the level of cortical hormone is very high, diuresis results in spite of normal production of antidiuretic hormone, and it appears that water balance can be maintained only by increased intake of water. From these findings Gaunt and his co-workers [22] concluded that the adrenal cortex hormones were necessary for diuresis, while the finer control of water exchange would depend on factors controlling thirst and the secretion of antidiuretic hormone. When the adrenal cortex hormones and antidiuretic hormone were reduced simultaneously, as in hypophysectomy, rapid diuresis was impossible, but it was rapidly restored by administration of cortical hormones. When the anterior pituitary remained after ablation of the posterior pituitary, polyuria resulted from multiple influences, one of which was thought to be the continued production of corticotropin (ACTH) with resultant production of adrenal cortex hormone in the absence of antidiuretic hormone.

Administration of adrenal cortex hormone may result in the seeming paradox of simultaneous edema and diuresis. The following proposed tentative chain of events which best explains this paradox was proposed by Gaunt and his co-workers.[22] First, retention of sodium and chloride ions with osmotic retention of water occurs. This causes expansion of the extracellular fluid compartment, which may progress to frank edema. In the early stages of therapy with adrenocortical hormone, osmotic retention of water may mask the diuretic effect of adrenal hormones which is brought about by decreased tubular reabsorption of water. With the continued retention of salt, thirst is stimulated. The increased intake of water in the presence of decreased tubular reabsorption leads finally to a diabetes-insipidus-like state. With these factors operating, it would be possible to have simultaneously (1) retention of water with an expanded extracellular space and even edema and (2) increased excretion of water. These investigators also thought that the adrenocortical hormones prevented the accumulation of antidiuretic hormones by some unknown mechanism and so combated its antagonistic effects.

Thyroid Hormone.—The role of the thyroid in clinical water intoxication is difficult to evaluate. Gaunt, Cordsen, and Liling [23] found that rats with experimentally induced hyperthyroidism were more resistant to water intoxication than were untreated animals. This resistance, they said, resulted in part from the fact that hyperthyroid animals excreted less chloride in water diuresis than did normal ones. They also noted that the characteristic protective effects of hyperthyroidism were largely abolished by adrenalectomy. These experimental findings implied that much, if not all, of the protection against water intoxication afforded by hyperthyroidism was indirectly the result of adrenal activity. While no clinical counterpart to these experiments could be found, it is known that thyroid hormone affects the water metabolism of myxedematous patients, causing a diuresis, the mechanism of which is unknown.

Electrolyte Depletion.—Electrolyte depletion has been observed clinically to increase susceptibility to water intoxication. This is believed to result from (1) hypotonicity existing prior to administration of water and (2) decreased renal excretion of water from decreased renal blood flow.

TESTS BASED ON RESPONSE TO FORCED INTAKE OF WATER

Since the original studies on water intoxication the body response to water, in forced doses both large and small, has become the basis for a number of proposed diagnostic procedures and assays. McQuarrie and Peeler [24] in 1931 employed this principle in the betahypophamine-hydration test as a diagnostic aid in epilepsy. Robinson, Power, and Kepler [25] in 1941 used forced doses of water as a diagnostic procedure for adrenal cortex hypofunction; Pebranyi [26] in 1941 used them as an assay for cortical extracts; Hays [27] in 1943 used them as an assay for desoxycorticosterone; Schiller and Dorfmann [28] in 1943 used them as a test for urinary cortical materials, and Lichtman [29] in 1949 advocated forced-water dosage as a test of hepatic function.

CLINICAL REPORTS

In 1931 DeTakats [30] called attention to the potential danger in postoperative patients of water intoxication which could result from the surgeon's order to "push fluids." In 1932 Arnold and Fay [31] concluded that in eclampsia the cerebral dis-

23. Gaunt, R.; Cordsen, M., and Liling, M.: Water Intoxication in Relation to Thyroid and Adrenal Function, Endocrinology **35**:105-111 (Aug.) 1944.

24. McQuarrie, I., and Peeler, D. B.: The Effects of Sustained Pituitary Antidiuresis and Forced Water Drinking in Epileptic Children: A Diagnostic and Etiologic Study, J. Clin. Invest. **10**:915-940 (Oct.) 1931.

25. Robinson, F. J.; Power, M. H., and Kepler, E. J.: Two New Procedures to Assist in the Recognition and Exclusion of Addison's Disease: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **16**:577-583 (Sept. 10) 1941.

26. Pebranyi, G.: Cited by Gaunt.[18]

27. Hays, H. W.: Cited by Gaunt.[18]

28. Schiller, S., and Dorfmann, R. I.: Cited by Gaunt.[18]

29. Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, Ed. 2, Philadelphia, Lea & Febiger, 1949, pp. 311-312.

30. DeTakats, G.: Push Fluids; the Surgeon's Postoperative Order, Am. J. Surg. **11**:39-44 (Jan.) 1931.

31. Arnold, J. O., and Fay, T.: Eclampsia: Its Prevention and Control by Means of Fluid Limitation and Dehydration, Surg., Gynec. & Obst. **55**:129-150 (Aug.) 1932.

turbances might result from water intoxication, the cause of which was in some way related to the fundamental disease process. The first frank case of water intoxication was reported in 1935 by Helwig, Schutz, and Curry.[11] The patient was a 50-year-old woman, the nature of whose condition was unrecognized before death. She absorbed 9 liters of tap water by proctoclysis within 30 hours after simple cholecystectomy and died in convulsions.

In 1938 Helwig and his co-workers [32] reported a second case in a woman, resulting from the absorption of 8,250 cc. of water by proctoclysis within 40 hours after operation. Though she was convulsing and moribund when administration of 5% sodium chloride solution was begun intravenously, improvement was prompt. Some symptoms continued, and she remained comatose for four or five days but recovered without residua. While acutely ill, she had a carbon dioxide combining power of the plasma of 32 vol. %.

Barahal [33] in 1938 reported the case of a female patient with schizophrenic reactions (dementia praecox) who had edema, coma with muscular twitchings, and convulsions with gradual recovery over a five-day period. After recovery she admitted drinking excessive amounts of tap water, and Barahal expressed the belief that her symptoms had resulted from water intoxication.

Trusler, Egbert, and Williams [34] in 1939 reported the case of a 2-year-old girl who had received extensive burns and was treated with large quantities of fruit juices, alkalies, and calcium by mouth and isotonic sodium chloride solution and dextrose intravenously. Her condition remained good for 48 hours, but on the third day she became stuporous. She could be roused, however, and would take large amounts of water and fruit juice orally. Generalized edema developed, and at the end of 72 hours she went into convulsions which continued until her death 6 hours later. Blood drawn near the time of death showed profuse hemolysis of red cells, practically no clot formation, and a concentration of blood chloride of 140 mg. per 100 cc. (39 mEq. per liter). Necropsy performed promptly after death revealed tremendous water-logging of all tissues, with quantities of free fluid in the abdominal and chest cavities. In this case, the authors considered water intoxication a complicating factor and possibly a lethal one.

Gamble,[35] in his lecture syllabus, presented data on an infant exhibiting anuria for six days following administration of a sulfonamide. During this time the infant was given dextrose solution in large excess over his insensible expenditure of water from skin and lungs. On the fifth day of anuria symptoms of water intoxication appeared, and plasma values of 108 mEq. per liter for sodium, 67 mEq. per liter for chloride, and 21 mEq. per liter for bicarbonate were found. In this patient there was a spontaneous recovery of renal function, with rapid restoration of normal ionic

32. Helwig, F. C.; Schutz, C. B., and Kuhn, H. P.: Water Intoxication: Moribund Patient Cured by Administration of Hypertonic Salt Solution, J. A. M. A. **110**:644-645 (Feb. 26) 1938.

33. Barahal, H. S.: Water Intoxication in a Mental Case, Psychiatric Quart. **12**:767-771 (Oct.) 1938.

34. Trusler, H. M.; Egbert, H. L., and Williams, H. S.: Burn Shock: the Question of Water Intoxication as a Complicating Factor; Blood Chemical Studies and Report of an Extensive Burn Treated by Repeated Transfusions of Blood and Blood Plasma, J. A. M. A. **113**:2207-2213 (Dec. 16) 1939.

35. Gamble, J. L.: Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid: A Lecture Syllabus, Cambridge, Mass., Harvard University Press, 1947, Chart 35-C.

concentration before more than a small part of the theoretical requirement for 1.8% solution of sodium chloride could be provided.

Brown and his co-workers [36] in 1943 reported nine cases of overhydration of patients receiving artificial fever therapy. Three of these were presented in some detail. In two, edema from excess of salt and water developed, but they had good tolerance for this overloading. In contrast, in the third patient, who apparently received an excess of water but no salt, water intoxication developed. After 10 hours of treatment she began to have "grand mal seizures" which passed into "status epilepticus," at which time the treatment was terminated. By this time her intake was 5,300 cc. of fluid, and the output of urine was 80 cc. with moderate sweating. She was given anticonvulsants intramuscularly and intravenously and finally a general anesthetic agent which apparently controlled the attacks. The specific gravity of the plasma determined during treatment was 1.0175, "the lowest ever observed." Fluids were withheld, diuretics given, and she excreted 1,200 cc. of urine in the next 12 hours. The authors concluded, "This patient was not outwardly edematous at any time, the overhydration apparently being mostly within the circulating system and brain. This situation may be very confusing to the clinician, for the appearance is all in favor of dehydration."

COMMENT

Rowntree [1] expressed the belief that the symptoms in water intoxication are probably caused by increased intracranial pressure from disturbance in the "salt to water equilibrium of the body and of the central nervous system." Experimental evidence against the causal role of increased intracranial pressure was offered by Keith,[13] who found that a large excess of water in rabbits increased the fluid content of their brains and their susceptibility to convulsions induced by thujone, while a maximal increase in the fluid content of rabbits' brains resulting from administration of hypotonic sodium chloride solution (0.45%) did not increase their susceptibility to thujone convulsions. Kubie [37] found increases in intracranial pressure of similar magnitude in dogs' brains following infusions of distilled water, 0.47% sodium chloride solution, and 0.9% sodium chloride solution. These findings would support the contention that the difference in body response to excesses of water and sodium chloride solution does not depend on a difference in intracranial pressure.

A statement of the now widely accepted theory of the pathogenesis of water intoxication follows: Excessive water is administered either orally, parenterally, or by proctoclysis. This results in an initial dilution of the blood and interstitial fluid, which constitute the extracellular compartment, and results in a reduction of the extracellular concentration of electrolyte, or hypotonicity. An osmotic gradient is established between the extracellular and intracellular spaces. This causes water to move from the extracellular space of lesser electrolyte concentration across the cell membrane and into the cell space of greater electrolyte concentration. With this increasing excess of intracellular water and consequent intracellular hypotonicity, there is progressive dysfunction of the cells. The most pronounced symptoms are

36. Brown, H. R., Jr.; Clark, W. F.; Jones, N.; Walther, J., and Warren, S. L.: Relationship of Dehydration and Overhydration of the Blood Plasma to Collapse in Management of Artificial Fever Therapy, J. Clin. Invest. **22**:471-485 (July) 1943.

37. Kubie, L. S.: Intracranial Pressure Changes During Forced Drainage of Central Nervous System, Arch. Neurol. & Psychiat. **16**:319-328 (Sept.) 1926.

manifested by neuronal dysfunction of the central nervous system, with muscle twitching, coma, and convulsions, and eventually death results if the disturbance progresses. The essential condition upon which such a pattern of events depends is the relative hypotonicity of the extracellular fluids when compared with the intracellular. This extracellular hypotonicity results from excessive administration of water. That a change in the tonicity of the body fluids is not the only factor that is operating was proved by Gaunt and his co-workers [22] when they demonstrated definite increased resistance to water intoxication in adrenalectomized nephrectomized animals following administration of desoxycorticosterone acetate. Since desoxycorticosterone acetate could not affect water metabolism by increasing water excretion in nephrectomized animals, an action on the distribution of body fluid was postulated as an added protective factor against water intoxication.

The infrequency with which edema accompanies water intoxication is best explained by the fact that the extra water retained, which need not be great to produce symptoms, is theoretically distributed in equal proportion to the vascular, interstitial, and intracellular spaces as a result of proportional expansion of each. Symptoms usually occur before there is expansion of the interstitial space of a magnitude necessary to produce edema. This course of events may be contrasted with that which results from excessive administration of isotonic sodium chloride solution. The sodium chloride solution causes essentially an expansion of the extracellular space but does not alter the osmotic gradient because it does not alter isotonicity, so there is no significant increase in intracellular water. Edema becomes evident with increasing extracellular expansion and may progress to extreme degree with no other symptoms. This expansion of extracellular space constitutes an increased vascular load, which may be reflected by pulmonary edema and circulatory failure.

Though hypotonicity or relative hypotonicity of the extracellular fluid is the indispensable condition in water intoxication, the absolute concentration of body electrolyte is not as important as is the rate at which body tonicity is reduced. As an example, a chronically ill patient may have a serum sodium level of 120 mEq. per liter and not suffer from water intoxication. In contrast, if the serum sodium level is lowered rapidly from 140 to 135 mEq. per liter by dilution with water, the patient is likely to have the symptoms of water intoxication. The sudden retention of a relatively small volume of water may produce symptoms. This excess of water may result from a water dosage exceeding the maximal ability of the normal kidney to excrete water or from a normal water dosage in the presence of impaired ability of the kidney to excrete water.

Excess of water within the cell is usually considered an acute problem, but Peters [38] and Schroeder [39] have expressed the belief that relative excess of water within the cell may be a subacute or even a chronic disturbance. The tentative schemes of pathogenesis in Peters' salt-depletion syndrome and Schroeder's low-sodium syndrome are similar. Schroeder reported upon patients who became salt-depleted as a result of receiving mercurial diuretics which act by blocking the

38. Peters, J. P.: The Treatment of Salt Depletion, Editorial, Surgery **24**:568-570 (Sept.) 1948.

39. Schroeder, H. A.: Renal Failure, Associated with Low Extracellular Sodium Chloride: Low Salt Syndrome, J. A. M. A. **141**:117-123 (Sept. 10) 1949.

reabsorption of electrolyte by the renal tubules. Because of this loss of electrolyte, extracellular hypotonicity resulted, with water moving into the cells. Both investigators expressed the belief that the excess of intracellular water and resultant cellular dysfunction are responsible for the renal and cardiac dysfunction with attendant symptoms. Beneficial response to the use of hypertonic sodium chloride solution, which they advocated as treatment, would militate in favor of this concept of pathogenesis.

The treatment of water intoxication is by stopping the administration of water. In mild cases recovery may occur spontaneously as a result of diuresis or insensible loss of water. Administration of hypertonic sodium chloride solution has been advocated in severe cases because it quickly increases the reduced tonicity of the extracellular fluid. This reverses the osmotic gradient, and water begins to move out of the cells into the extracellular space. A small amount of hypertonic sodium chloride solution will often relieve the symptoms, and in treating water intoxication only enough hypertonic sodium chloride solution should be given to relieve the symptoms; otherwise, serious overloading of the circulatory system may result from the sudden movement of water from the cells back into the extracellular space. This may cause congestive heart failure and pulmonary edema. Sodium chloride in 2 to 10% solutions has usually been advocated. If hypertonic sodium chloride solution is not immediately available, treatment can be started with isotonic sodium chloride solution.

SUMMARY

The subject of water metabolism in water intoxication has been reviewed. Clinical reports of water intoxication and of the results of tests based on forced dosage of water have been summarized. It is pointed out that the pathophysiology of water intoxication is that excessive intake of water dilutes the intravascular and interstitial fluid resulting in an osmotic gradient which moves water into the cell. Excessive water in the cell results in dysfunction, causing typical symptoms, such as nausea, vomiting, muscle twitching, convulsions, coma, and, if uncorrected, ultimately death. The possibly related conditions of Peters' salt-depletion syndrome and Schroeder's low-sodium syndrome have been discussed.

SCARLET FEVER

Evaluation of Continuous and Intermittent Penicillin Therapy

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SINCE 1945 when penicillin became available for general use, several investigators have reported on its use in the treatment of scarlet fever. Although there has been general agreement on the satisfactory therapeutic role of penicillin, there is no moderately close agreement as to method of administration, type of agent used, and duration of treatment. It is felt that a satisfactory standardization of treatment might be suggested by a correlation of our results with those of other investigations.

Our objective is twofold: first, to report the results of a critical clinical investigation of the effect of penicillin in the treatment of 386 scarlet fever patients, and second, to review briefly the current opinions of present-day writers in this field.

CLINICAL MATERIAL

The study included 386 patients whose duration of illness was four days or less before hospitalization. There were 185 males and 201 females in the group. All were hospitalized immediately after the appearance and discovery of the rash. In 44.9% (163 patients) there was an acute prodromal onset of the disease 24 hours or less before admission. Seventy-three per cent (284 patients) had been ill for less than 48 hours before admission. Only 7% (28 patients) had been ill for as long as four days.

One hundred nineteen patients received 20,000 to 40,000 units of an aqueous solution of penicillin intramuscularly every three hours for seven days. The other 267 patients were treated with 300,000 units of penicillin procaine intramuscularly every 24 hours for seven days. In this paper the abbreviated term penicillin-3 will be used henceforth to refer to injections of penicillin given at intervals of every three hours. Similarly, penicillin-24 will be used to refer to injections of penicillin given every 24 hours.

The age levels (Table 1) in both the penicillin-3 and penicillin-24 series were identical. Eighty per cent (300 patients) were between the ages of 3 and 10 years. The youngest patient was 4 months old, and the oldest patient was 36 years old. Scarlet fever in a patient under 1 year of age was rare; there were four such cases in this study, an incidence of 1%. Three patients were older than 20 years, an incidence of 0.7%

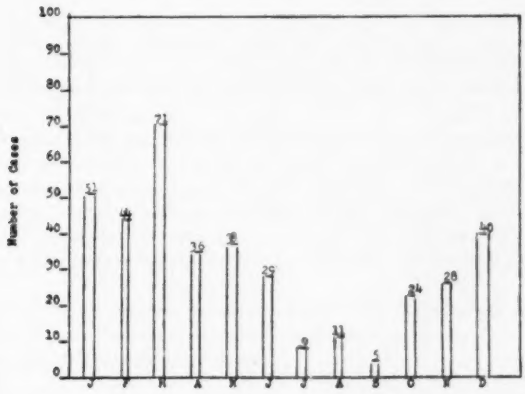
As shown in the accompanying chart 56% of the patients were admitted during the winter months, from December through March, and less than 7% during the summer months, from July through September. The illness occurred in the spring in 26% of the cases, and during the autumn months in 23%.

In less than one-fifth of the patients admitted to the Charles V. Chapin Hospital with scarlet fever was a history of recent exposure to the disease elicited (Table 2).

From the Department of Pediatrics, Charles V. Chapin Hospital and the Rhode Island Hospital.

TABLE 1.—*Age Groups of Scarlet Fever Patients Treated with Penicillin*

	Years					
	0-2	3-5	6-10	11-15	16-20	Over 20
Penicillin-3	9	46	42	20	0	1
Penicillin-24	26	94	117	20	8	2
Total	35	140	160	40	8	3



Seasonal incidence of scarlet fever by months.

TABLE 2.—*Bacteriologic Findings and Other Data for Penicillin-Treated Patients*

	Penicillin-3 20,000-40,000 Units Every 3 Hr., 119 Patients		Penicillin-24 300,000 Units a Day, 287 Patients	
	No.	Per Cent	No.	Per Cent
Bacteriologic findings (Streptococcus pyogenes)				
Throat culture positive on admission	68	57	154	58
Nose culture positive on admission	15	13	34	13
Total patients treated before admission	17	14	50	19
Throat culture positive	5	29	7	14
Nose culture positive	0	0	0	0
Throat culture positive 24 hr. after admission	13	11	26	10
Throat culture positive 48 hr. after admission	4	3	9	3
Throat culture positive on discharge	0	0	0	0
Duration of fever				
No fever observed	25	21	53	20
24 hr.	36	30	109	41
2 days	38	32	62	23
3 days	17	14	24	9
4 days	3	3	13	5
5 days	0	0	6	2
8 days	0	0	0	0
Other findings				
Strawberry tongue	87	73	176	66
History of exposure to scarlet fever	25	21	50	19

METHOD OF STUDY

An attempt was made to classify each newly admitted patient according to the degree of severity of the illness. The classification severe included those patients who had (1) temperature greater than 102 F., (2) white blood cell count of 15,000 cells per cubic millimeter or greater, and (3) symptoms of severe toxicity, such as headache, nausea and vomiting, arthralgia, and myalgia. Patients whose illness was classified as moderate had (1) temperature between 100 and 102 F., (2) white blood cell count between 10,000 and 15,000 per cubic millimeter, and (3) two or three of the above-named toxic symptoms. The illness was classified as mild when a patient had (1) temperature below 100 F., (2) normal white blood cell count, and (3) minimal or no signs of toxicity (Table 3).

The clinical appearance of the patient with regard to amount of discomfort in the pharynx, accompanying redness, swelling, exudate, hypertrophy of pharyngeal and cervical lymphoid tissue, rash, and petechial hemorrhagic manifestations contributed significantly to the classification and correlated well with the three major criteria for calling scarlet fever severe, moderate, or mild.

Nose and throat cultures were done daily until negative and then twice weekly unless otherwise indicated. An average of eight throat cultures were taken for each patient. Urine was examined three times weekly. Complete blood count was done on admission and then weekly. Studies of blood chemistry, sugar content, nonprotein nitrogen, electrocardiograms, erythrocyte sedimentation rate, etc., were performed whenever the condition of a patient made them pertinent. Daily physical examinations were done; rectal temperatures were recorded

TABLE 3.—*Classification of Patients According to Severity of Illness*

	Severe	Moderate	Mild
Penicillin-3	18	67	34
Penicillin-24	28	127	112

every four hours. The condition of the throat, disappearance of the rash, desquamation, and development of secondary complications were duly noted. Except when persistent complications demanded further observation, each patient was hospitalized for 21 days.

RESULTS

Effect of Penicillin on Fever.—Table 2 demonstrates the effect of penicillin on the duration of fever. Seventy-eight patients had a temperature below 100 F. on admission. Penicillin-3 and penicillin-24 gave equally good results. In 37% of the patients, temperatures became normal within 24 hours after therapy was started. After 48 hours 62% of the patients treated with penicillin-3, and 64% of those treated with penicillin-24 had a normal temperature. In more than 95% of all cases, fever disappeared within 72 hours after admission.

Effect of Penicillin on Rash and Strawberry Tongue.—The duration of the rash was not affected by either method of penicillin therapy. Sixty-five per cent of the exanthemas disappeared between the third and fifth hospital day. The rash persisted for more than 6 days in 8% of the patients, and no rash was noted in any patient after the 10th day in the hospital. Typical strawberry tongue was seen in 70% of the patients (Table 2).

Effect of Penicillin on Urinary Findings.—The urine of each patient was frequently collected and carefully analyzed (Table 4). No red blood cells were seen in the urine of any patient, and no instance of true glomerulonephritis was found in spite of careful follow-up study for elevated blood pressure, retention of nonprotein nitrogen, and hematuria.

Several instances of mild albuminuria and moderate numbers of white blood cells were found. In the penicillin-3 group, 37% of the patients had albumin in the urine, 24% had white blood cells, and 19% exhibited both albumin and white blood cells in the urine. Albumin was found in 40% of the penicillin-24 group, white blood cells in 20%, and both albumin and white blood cells in 16% of the urine examined. Usually these mild urinary changes occurred during the first week of hospitalization. All patients, when discharged, had had normal urine for not less than one week.

Bacteriologic Results.—Both penicillin-3 and penicillin-24 are effective in eradicating the beta hemolytic Streptococcus organism from the nose and throat of scarlet fever patients. In 58% of the cases (222 patients) throat swabs taken on admission produced positive cultures on a media of blood agar. Similarly, 13% (49 patients) of the cultures done from nasal discharge on admission were positive. The rate of disappearance of streptococci from the nasopharynx affords a true measure of the

TABLE 4.—*Data on Complications and Urinalyses of Penicillin-Treated Patients*

	Penicillin-3 20,000-40,000 Units Every 3 Hr., 119 Patients		Penicillin-24 300,000 Units a Day, 267 Patients	
	No.	Per Cent	No.	Per Cent
Complications				
Present on admission	7	6	9	2.3
Developed following therapy	11	9	23	9
Nonsuppurative	9	7.3	21	8
Suppurative	2	1.7	2	0.8
Late sequelae	0	0	0	0
Results of urine examinations				
Albumin (5-100 mg.)	44	37	108	40
White blood cells	29	24	55	20
Red blood cells	0	0	0	0
Combination of two of above abnormalities	22	19	44	16

effectiveness of penicillin therapy in eliminating the Streptococcus. In the penicillin-3 group, 89% after 24 hours, and 97% after 48 hours, were free of the Streptococcus organisms in the nose and throat. In the penicillin-24 treated group, 90 and 97% of the patients no longer harbored organisms in the nasopharynx after 24 and 48 hours of treatment, respectively.

Sixty-seven patients received some form of medication at home before the diagnosis of scarlet fever was made. The quantity of antimicrobial agents taken at home in no case was reported as exceeding one intramuscular injection of penicillin, oral use of four tablets of a sulfonamide or penicillin, or 2 teaspoonsful of a liquid sulfonamide preparation. In 17% of this "treated" group of patients, positive cultures for Streptococcus pyogenes were obtained from the pharynx, but in none were streptococci cultured from the nose.

Complications.—Patients Treated with Penicillin-3: Complications were present in seven patients on admission. One patient exhibited a suppurative otitis media from which was cultured Streptococcus pyogenes. In another patient roentgenologic findings were consistent with antrum sinusitis. Five patients had infected tympana membrana without suppuration or culture positive for organisms. One patient had an abscess of the thumb from which Streptococcus pyogenes was cultured, but the

abscess was considered to be the source rather than a complication of scarlet fever. The discharge from the ear cleared in three days, the painful antrum subsided rapidly, tenderness disappeared, and a roentgenogram showed a normal mucosal pattern on the eighth day. No supplementary medication was employed.

There were 11 patients (9%) in whom complications developed after the initiation of therapy and after the temperature had been normal for at least 48 hours. In two suppurative otitis media developed from which hemolytic streptococci were recovered. The first occurred on the sixth hospital day. Penicillin-3 (30,000 units every three hours) was continued until the ninth day, in addition to sulfadiazine every six hours by mouth for three days. Normal temperature and benign condition of the nasopharynx and the ears were found on the 10th day. In the second patient a temperature of 103.6 F. developed on the third day, with an increase in the size of the anterior cervical lymph nodes. The temperature rose to 104 F., and the left ear began to drain bloody serous pus 24 hours later. With continuation of penicillin-3, the infection cleared completely by the seventh day. Both patients were discharged on the 21st hospital day. The other nine patients in whom fever developed had been afebrile for several days. The rise in temperature occurred on the 10th, 11th, 13th, 17th, 18th (4 patients), and 21st days. In five instances, hemolytic streptococci were cultured from the pharynx. Penicillin-3 was then administered for 24 hours. Repeat daily cultures from the pharynx for one week did not recover any more streptococci.

Patients Treated with Penicillin-24: Nine patients (2.3%) were admitted to the hospital with preexisting complications; 4 had suppurative otitis media, and the others had catarrhal otitis media. No further complications occurred in these nine patients, and there were no relapses.

In 34 patients an elevation of temperature developed after they had been afebrile for several days. It is interesting to note that in 11 of them a concomitant infectious disease developed owing to exposure prior to admission. In one patient pyuria developed on the ninth hospital day, with the patient complaining of right lower quadrant pain and dysuria. Examination of the urine showed moderate numbers of white blood cells and elevation of albumin, but no organisms were found upon culture. This patient ran a low-grade fever with a temperature of 100 to 101 F. After treatment with a sulfonamide compound (gantrisin®) by mouth, the temperature subsided to normal in six days. Pyuria was seen in one patient on the 14th day and subsided after two days of supportive therapy. Three patients with catarrhal otitis media were treated expectantly, with good results. In 17 patients an elevation in temperature developed between the 16th and 19th hospital days. A mildly reddened pharynx and positive cultures for hemolytic streptococci were observed in four instances. No cause for the transient elevation of temperature was found in the others.

COMMENT

Results in the treatment of scarlet fever were equally good with penicillin-24 as with penicillin-3. Ninety per cent of all patients were afebrile 72 hours after penicillin therapy was started; and more than 90 per cent were free from Streptococcus pyogenes within 24 hours. The effectiveness of both penicillin regimens may be partially explained in several ways. Scarlet fever has been a relatively mild disease for the past 10 years; in only 12% of our patients was the illness classified

as severe. The extreme sensitivity of Streptococcus pyogenes to penicillin is well known. Sixty-seven patients (17%) received some form of medication before hospitalization. Seventeen per cent of the "treated" patients, as compared to fifty-eight per cent of the untreated patients, had throat cultures positive for Streptococcus pyogenes on admission, and in none of the so-called "treated" patients were streptococci cultured from the nose.

The rapid elimination of most of the infecting organisms by penicillin shortens the length of acute sickness and the duration of toxemia. Early and frequent relapses are noted when the use of penicillin is discontinued after two or three days. It may be that some bacteria remain in the nasopharynx inaccessible to culture for several days after penicillin therapy and become active again when the drug is withdrawn too soon. Jersild [1] treated 1,000 patients with scarlet fever with 90,000 to 150,000 units of penicillin intramuscularly twice a day for six days. Nearly all the patients were rid of hemolytic streptococci in the nose and throat within 48 hours. Complications appeared in 5.5%, and only 4% of the patients harbored hemolytic streptococci at the end of treatment. Treatment was then arbitrarily shortened from six to three days without changing the dosage. Eighteen patients treated in this manner all became free of streptococci within 48 hours after the start of treatment. Within a few days, however, hemolytic streptococci were again cultured from the nasopharynx with increasing frequency. Eleven of the eighteen patients still harbored hemolytic streptococci when discharged from the hospital, and in seven (39%) of these complications developed subsequently. Jersild concluded that the "length of treatment is directly related to the results obtained with penicillin in scarlet fever."

One of us (E. J. W.) treated 300 scarlet fever patients in 1940, alternate patients receiving a sulfonamide. It was concluded that the sulfonamide did not materially reduce the complications.

In the present group of patients, penicillin effectively reduced the number of complications. In 8% of the patients nonsuppurative complications developed after treatment was stopped. With penicillin-3 treatment suppurative complications occurred in 1.7% of the cases, and with penicillin-24 treatment suppurative complications following treatment developed in 0.8% of the cases. There were no late sequelae in any patients. Thirty-seven per cent of the penicillin-3 group and 40 per cent of patients treated with penicillin-24 showed a transient albuminuria during the first week in the hospital. No patient demonstrated red blood cells in the urine; there were no elevations of blood pressure. In no case was acute glomerulonephritis diagnosed. A very occasional and transient systolic apical heart murmur was heard in several patients on admission but subsided before discharge. Repeated erythrocyte-sedimentation studies and electrocardiograms failed to reveal a single instance of true rheumatic fever. It was concluded, therefore, that penicillin may have assisted, when combined with bed rest, in reducing the number of early and late complications and sequelae in scarlet fever. The reduction in frequency of injections to once daily is sufficient to prevent the reappearance of streptococci provided penicillin therapy is continued for seven days.

1. Jersild, T.: Penicillin Therapy in Scarlet Fever and Complicating Otitis, Lancet **1**:671 (May 1) 1948.

REVIEW OF THE LITERATURE

At the United States Naval Hospital, Treasure Island, San Francisco,[2] 118 scarlet fever patients were studied. Several schemes of penicillin therapy were evaluated. In all cases there was good clinical response in that the temperature dropped to normal and there was marked symptomatic improvement in 24 to 48 hours. The investigators concluded that administration of 480,000 units of penicillin over an eight-day period is a satisfactory method for the treatment of scarlet fever and for preventing the establishment of a Streptococcus-pyogenes-carrier state in convalescent patients.

One hundred sixteen patients studied by Hoyne [3] each received an average of 499,823 units of penicillin over a period of 5.4 days. In the same study 312 patients received no specific therapy, 69 received convalescent serum, and 48 were treated with sulfonamide compounds. In the patients treated with penicillin, fever lasted 3.46 days and the rash 2.93 days. There were 15.51% complications following penicillin therapy and 37% and 31% complications following treatment with convalescent serum and sulfonamide compounds, respectively. However, the authors concluded, "Penicillin's customary method of administration must still be regarded as an obstacle in its use."

Hirsh,[4] in the first of two reports, compared the value of penicillin in the treatment of scarlet fever with that of sulfadiazine. Several different penicillin dosage schedules were employed, with 50,000 units every six hours for five days established as the routine dose. In 9% of the patients treated with penicillin complications developed and in 31% of the patients treated with sulfadiazine complications developed. Twenty-six per cent of the patients entered the hospital with preexisting complications, consisting in most cases of otitis media and cervical adenitis. All these complications cleared with penicillin therapy. Hirsh [5] treated 86 patients with 25,000 units of regular penicillin every three hours for five days and compared their course with that of 123 patients given only symptomatic care. The incidence of complications was 7% in the penicillin-treated group, compared with 26% in the group treated symptomatically. The streptococcic-carrier state was present in 8% of the penicillin group, upon discharge from the hospital, and in 82% of the group treated symptomatically.

Landon and Greenfield [6] treated 245 patients and gave either penicillin every three hours for 10 days, 60 cc. of gamma globulin intramuscularly on admission, or antitoxin soon after arrival. Three and one-half times as many complications occurred in the patients treated with antitoxin as in those treated with gamma globulin.

2. Epidemiology Unit No. 82, U. S. Naval Hospital: Observations on the Treatment of Scarlet Fever with Penicillin, Am. J. M. Sc. **211**:417-420, (April) 1946.

3. Hoyne, A. L., and Brown, R. H.: Penicillin for Scarlet Fever, J. A. M. A. **133**:661 (March 8) 1947.

4. Hirsh, H. L.; Dowling, H. P., and Sweet, L. K.: Treatment of Various Infections with Penicillin X, with a Preliminary Note on the Value of Penicillin X in Scarlet Fever, Ann. Int. Med. **25**:78 (July) 1946.

5. Hirsh, H. L.; Rotman-Kavka, G.; Dowling, H. F., and Sweet, L. K.: Penicillin Therapy of Scarlet Fever: Comparison with Antitoxin and Symptomatic Therapy, J. A. M. A. **133**:657 (March 8) 1947.

6. Landon, J. F., and Greenfield, N.: Occurrence of Complications in Scarlet Fever Treated with Penicillin, Antitoxin and Gamma Globulin, Am. J. Dis. Child. **76**:380 (Oct.) 1948.

Among the penicillin-treated patients, early complications were (1) acute purulent otitis media on the 2d day, (2) epidemic arthritis on the 5th day, and (3) cervical adenitis on the 12th day. Late complications, all on the ninth day, were lobar pneumonia, tonsillitis, and acute purulent otitis media.

Stammbach's [7] conclusions are based on the study of 100 patients, 50 of whom were given 2,000 units of penicillin per kilogram of body weight daily at three-hour intervals for seven days. Most children became afebrile between the fourth and sixth days, with or without penicillin, and there was no difference in the time of disappearance of the exanthem. Discharge was usually on the 35th day. In contrast to most investigations, he reported 46% complications for the penicillin-treated group and only 16% for the control group.

Weinstein [8] treated 167 scarlet fever patients with penicillin and determined the incidence of rheumatic fever and glomerulonephritis. One hundred twenty-seven patients received 15,000 units of crystalline penicillin G intramuscularly every three hours for 10 days. Forty patients were given 100,000 units of penicillin orally every three hours for 10 days. Twelve patients (7.17%) of the entire series who received penicillin (i. e., 2 orally and 10 intramuscularly) had laboratory or clinical manifestations suggestive of acute rheumatic fever. Six patients (3.52%) of the same group showed evidence of acute diffuse glomerulonephritis as a complication. In a later report, Weinstein [9] compared the symptomatic treatment with that of gamma globulin and penicillin in scarlet fever. No patient was admitted to this study who had had scarlet fever for more than 48 hours, and all patients were kept in the hospital for a minimum period of three weeks. One hundred two patients received symptomatic treatment; one hundred three were given globulin; and fifty were treated with penicillin, 15,000 units intramuscularly every three hours for 10 days. Most of the patients treated with penicillin were free of Streptococcus pyogenes in the nose and throat within five days after initiation of therapy. The rash persisted for approximately four to five days. Patients lost all discomfort in the throat and pharynx in from one to three days, and in 14 patients who were treated with penicillin, bacteriologic relapse occurred after cessation of therapy. Detailed data regarding the complications in the patients treated with the three regimens demonstrated the lack of suppurative sequelae in patients treated with penicillin. No instance of proved rheumatic fever was found in those who received penicillin but two patients were classified as suspects. Gamma globulin, contrary to Landon's [6] findings, exerted little if any effect on the development of suppurative and nonsuppurative complications. The only instance of acute glomerulonephritis occurred in the group receiving symptomatic treatment.

In his latest report, Weinstein [10] treated 117 patients with scarlet fever with crystalline penicillin G either orally or parenterally twice a day for periods of 7 and

7. Stammbach, H., and Larcher, F.: Penicillin in Scarlet Fever, Helvet. paediat. acta **3**:412 (November) 1948.

8. Weinstein, L.; Bachrach, L., and Boyer, N. H.: Observations on the Development of Rheumatic Fever and Glomerulonephritis in Cases of Scarlet Fever Treated with Penicillin, New England J. Med. **242**:1002 (June 29) 1950.

9. Weinstein, L., and Potsubay, S. F.: A Comparison of "Symptomatic Treatment," Gamma Globulin, and Penicillin in the Treatment of Scarlet Fever, J. Pediat. **37**:291 (Sept.) 1950.

10. Weinstein, L., and Daihos, G.: The Treatment of Scarlet Fever with Crystalline Penicillin G Administered Orally or Parenterally Twice a Day, Am. Pract. **2**:60 (Jan.) 1951.

10 days. Five groups of approximately 20 patients each received penicillin every 12 hours in the following dosages, respectively: 250,000 units intramuscularly for 10 days; 250,000 units orally for 10 days; 150,000 units intramuscularly for 10 days; 150,000 units orally for 7 days, and 100,000 units intramuscularly for 7 days. He concluded that the administration of penicillin G intramuscularly or orally twice a day in scarlet fever was satisfactory if large enough quantities were used. A total of 250,000 units given either parenterally or by mouth every 12 hours for 10 days appeared optimum. Suppurative complications (20%) appeared when 100,000 units of penicillin was given parenterally twice a day and were absent when 250,000 units was given every 12 hours for 10 days.

CONCLUSIONS

A clinical analysis of 386 scarlet fever patients treated with penicillin is presented.

Procaine penicillin, 300,000 units given intramuscularly once daily, was found to be as effective in the therapy of scarlet fever as was an aqueous solution of penicillin G given intramuscularly every three hours in doses of 20,000 to 40,000 units. All patients were treated with the antibiotic for seven days.

The relative mildness of scarlet fever during the past years and the extreme sensitivity of the hemolytic Streptococcus organism to penicillin have combined to eliminate the mortality rate and to reduce significantly the incidence of early and late complications in scarlet fever.

ACETIC ACID AEROSOL IN TREATMENT OF PURULENT BRONCHIECTASIS DUE TO PSEUDOMONAS AERUGINOSA

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THE PURPOSE of this paper is to report the case of a patient with chronic bronchiectasis in which Pseudomonas aeruginosa was cultured repeatedly from the respiratory tract and in whom the use of an acetic acid aerosol produced marked clinical improvement after antibiotic therapy had failed.

Olsen [1] describes aerosols as mists of medicated solutions, and when such mists are inhaled by a patient the therapy is called aerosol therapy. He also states that if aerosol therapy has merit it is because of the topical effect exerted by the inhaled preparations on the bronchial mucosa and the mixing of the preparation with purulent bronchopulmonary secretions. The commonly encountered Gram-positive organisms to be found in bronchiectatic secretions are pneumococci, hemolytic and nonhemolytic streptococci and staphylococci. The common Gram-negative bacteria include Escherichia coli, Hemophilus influenzae, Aerobacter aerogenes, and Klebsiella pneumoniae. On many occasions Gram-negative bacteria are not isolated from sputum cultures until after the patient has been treated with penicillin aerosol. With continued treatment, resistant bacteria are likely to appear in bronchial secretions. Gram-negative bacteria are especially likely to become resistant to streptomycin.

In a study of otitis media, Davis,[2] in 1924, found that acetic acid readily eliminated P. aeruginosa. Ochs [3] successfully used an aluminum acetate and 2% acetic acid tampon for treatment of external otitis in 165 patients. Boiled household vinegar which contains about 5% acetic acid is used. Occasionally he used the vinegar in full strength as drops in the treatment of otitis externa due to P. aeruginosa. It is a well-established but not well-known fact that acetic acid acts almost specifically as a bactericidal agent against P. aeruginosa. It is frequently used as a wet dressing to overcome infections in contaminated surgical wounds, burns, and granulating osteomyelitic wounds due to this organism. A solution containing 1 to 2% acetic acid usually clears the malodorous green discharge in a few hours. There is no apparent damage to the tissue by this treatment.

The interest of Mr. O. L. Weiser, Bacteriologist, Fitzsimons Army Hospital, and Mr. F. W. Church, Director of the Division of Industrial Medicine, University of Colorado School of Medicine, is acknowledged.

1. Olsen, A. M.: Administration of Antibiotic Preparations by the Aerosol Method: A Critical Evaluation, M. Clin. North America **32**:1077 (July) 1948.

2. Smith, D. T.: Causes and Treatment of Otitis Media: I. Observations on 205 Cases Occurring in 613 Consecutive Hospital Admissions, Am. J. Dis. Child. **28**:1 (July) 1924.

3. Ochs, I. L.: Treatment of External Otitis: A Simple and Effective Technic, J. A. M. A. **142**:1361 (April 29) 1950.

Owen [4] demonstrated the bactericidal properties of acetic acid, particularly against Pseudomonas aeruginosa, Proteus vulgaris Hauser (Bacillus proteus), and other Gram-negative bacilli. He found that beef-heart-infusion broth with enough added acetic acid to produce a pH of 5.0 to 5.5 completely inhibited the growth of Gram-negative bacilli, although permitting the growth of streptococci and staphylococci; a pH of 4.5 with acetic acid would inhibit the growth of all organisms. He believed that this was due to the acetic acid and not to the lowered pH, since observations with hydrochloric acid or sulfuric acid were entirely unsuccessful.

In 1938 Gill [5] mentioned the use of 2% acetic acid in the treatment of external ear disease due to P. aeruginosa and later recommended it specifically in the treatment of infection with this organism.[6] The author has successfully treated two patients with otitis externa due to P. aeruginosa with full-strength household vinegar.

Bifulco [7] in May, 1949, reported what he described as the only case of pulmonary Bacillus pyocyaneus (P. aeruginosa) infection in an adult with recovery. The patient was treated with streptomycin aerosol and penicillin.

Since the acetic acid had such a bactericidal effect on Pseudomonas skin infections, its use seemed indicated in a pulmonary infection which had not responded to customary antimicrobial therapy. After consultation with Mr. F. W. Church, director of the Division of Industrial Medicine of the University of Colorado, it was decided that the following concentrations of acetic acid could be tried with a reasonable expectation that they would not be irritating to the respiratory tract: (*a*) 1 cc. of glacial acetic acid in a 1:1,000 solution to be used as an aerosol and (*b*) 2 tablespoonfuls (1 oz.) of vinegar to 1 qt. (1 liter) of water to be used as a steam vapor.

REPORT OF A CASE

History of Present Illness.—A 6½-year-old white girl, born Nov. 15, 1943, was first admitted to Fitzsimons Army Hospital on April 13, 1950. She had been well until November, 1945, when a nonproductive nocturnal cough developed and grew progressively worse. For three years the condition was diagnosed as chronic bronchitis. In December, 1948, the cough became productive of thick yellow sputum, and the child had a daily temperature ranging from 100 to 103 F. She was hospitalized, and it was noted that she had slight clubbing of the fingernails. There were crackling rales throughout the right lung and occasionally in the left lung posteriorly. She responded to penicillin therapy. The reaction to the tuberculin test, 1:100 dilution, was negative. Fibrocystic disease of the pancreas was ruled out by duodenal aspiration. Roentgenograms of the paranasal sinuses were normal. Bronchoscopic examinations were done on Feb. 7 and 14, 1949, at which times thick viscid purulent material came from both lungs. Culture of this material showed hemolytic Staphylococcus (coagulase positive), Neisseria catarrhalis, and Diplococcus. The bronchograms were reported as showing cylindrical bronchiectasis in the anterior portion of the left lower lobe and slight bronchiectasis in the right lower and upper lobes. She was treated with penicillin intramuscularly, penicillin and streptomycin aerosols, and aureomycin orally. On April 30 for the first time P. aeruginosa

4. Owen, C. R.: Acetic Acid Inhibition of Gram Negative Bacilli in Culture Media, J. Bact. **52**:353 (Sept.) 1946.

5. Gill, W. D.: Otomycosis: Some Remarks Concerning its Prevelance, Symptomatology and Treatment, Ann. Otol. Rhin. & Laryng. **47**:189 (March) 1938.

6. Gill, W. D.: Otomycosis, in Jackson, C., and Jackson, C. L.: Diseases of the Nose, Throat and Ear, Philadelphia, W. B. Saunders Company, 1945, p. 243.

7. Bifulco, E.: Pulmonary Bacillus Pyocyaneus (Pseudomonas Aeruginosa) Infection in and Adult with Recovery, New York J. Med. **49**:1195 (May 15) 1949.

was found on the throat culture, and the same organism was found upon culture of bronchoscopic aspiration in May. This organism was not sensitive to penicillin or streptomycin.

The patient was relatively well from May to July, 1949, when she had to be readmitted to a hospital for treatment of left midlung pneumonia. Oral administration of aureomycin and chloramphenicol had little effect on the temperature for 12 days. Material from bronchoscopic aspiration on Aug. 30 revealed P. aeruginosa and one acid-fast bacillus. Cultures of the gastric washings were negative for the tubercle bacillus. From Aug. 12 to Sept. 10 she lost 4 lb. (1.8 kg.), and her weight was down to 32½ lb. (14.7 kg.). A culture of secretions obtained from bronchoscopy on Sept. 13 revealed Klebsiella pneumoniae. She was treated with streptomycin by aerosol, sulfadiazine orally, and penicillin intramuscularly from Sept. 13 to Sept. 23. From Sept. 13 to Oct. 20 she was given a high-protein diet with added vitamins, an iron preparation, and liver extract intramuscularly, and she gained 7 lb. (3.2 kg.). On Feb. 20, 1950, a follow-up bronchogram showed what was reported as a cavity of 2.5-cm. diameter in the left lower lung and several suggestive small cavities in the right lower lung.

Hospital Course and Treatment.—The patient was admitted to Fitzsimons Army Hospital on April 13, 1950. Her only medication at this time was tripelennamine (pyribenzamine®) hydrochloride expectorant which relieved her coughing to some extent. The physical examination revealed a chronically ill girl, aged 6½ years, weight 38 lb. (17.2 kg.) with slight cyanosis of the lips and cyanosis with slight clubbing of the fingernails. There were some fine rales in the right lower lung field laterally. The blood pressure was 90/60. The laboratory work on admission revealed a white blood cell count of 15,500, with 53% neutrophiles and 47% lymphocytes. The hemoglobin was 13.6 gm., and there were 5,120,000 red blood cells. The sedimentation rate was 42 mm. in 60 minutes (Wintrobe). The throat culture showed abundant P. aeruginosa. The chest roentgenogram showed generalized, markedly increased bronchovascular markings with some peribronchial pneumonitis. There was a 2.5-cm. mottled density in the left lower lobe of the lung, plus some scattered iodized oil throughout both lung fields. From April 13 to May 3 the patient had a slight evening rise in temperature (100.5 F. rectally). On April 20 therapy was begun with 0.25 gm. of streptomycin intramuscularly twice a day, 50,000 units of streptomycin by aerosolization three times a day, 5 drops (5 minims) of potassium iodide in saturated solution three times a day, and postural drainage twice a day. The stools were positive for trypsin on a film digestion test. The electrocardiogram was normal. The reactions to the tuberculin test (purified protein derivative 2), the histoplasmin test, and the coccidioidin test were negative. On April 26 a bronchogram showed some dilatation and crowding of basic rami of the left lower lobe and some cylindrical dilatation of the bronchi in the right middle and upper lobes. Intramuscular administration of streptomycin was discontinued on the same day. The white blood cell count on May 3 was 18,350, with 69% neutrophiles, 28% lymphocytes, 2% eosinophiles, and 1% basophiles, and the sedimentation rate was 24 mm. in 60 minutes (Wintrobe). The throat culture on the same day showed abundant Klebsiella pneumoniae and P. aeruginosa. On May 10 aureomycin therapy was started in a dosage of 250 mg. orally twice a day. A bronchoscopic examination five days later revealed marked bilateral bronchopulmonary suppuration. On May 24 a high-protein, high-carbohydrate diet was instituted. From May 28 to June 11 the patient's temperature ranged from normal to 101.8 F. rectally. Oral administration of aureomycin was discontinued on May 31. Five days later the throat culture showed scant Neisseria species. Chloramphenicol (chloromycetin®) therapy was begun June 10 in a dosage of 250 mg. twice a day and was continued for nine days. On June 12 the white blood cell count was 22,650, with 65% neutrophiles, 25% lymphocytes, 2% monocytes, 7% eosinophiles, and 1% basophiles. Penicillin aerosol therapy was started on June 17, and beginning June 21 penicillin was administered intramuscularly in a dosage of 300,000 units for seven days. The day after intramuscular therapy was begun the patient's temperature ranged between 101 and 102.4 F. rectally but was normal the next day and remained normal until July 3. On June 24 there was added to the penicillin aerosol 0.25 gm. of streptomycin, and chloramphenicol therapy was started again in a dosage of 250 mg. twice daily. Bronchoscopy on June 26 revealed thick, foul sputum from all orifices, probably more from the left. From July 3 to Oct. 6 the patient had frequent temperature elevations up to 101 to 102.6 F. rectally. The use of penicillin aerosol and streptomycin was discontinued on July 12, and beginning Aug. 1 five-tenths gram of sulfadiazine was administered three times

a day for three days. On Aug. 3 the throat culture revealed abundant Pseudomonas. The next day the white blood cell count was 13,200, with a normal differential distribution. The sedimentation rate on Aug. 10 was 38 mm. per 60 minutes (Wintrobe). Chloramphenicol therapy was discontinued on Aug. 19, and 10 days later the use of potassium iodide drops was discontinued. A bronchoscopic examination on Aug. 30 reaveled thick, purulent, foul-smelling sputum from all orifices. The culture of this secretion showed abundant K. pneumoniae and P. aeruginosa. On Sept. 6 intramuscular penicillin therapy was started in a dosage of 300,000 units daily, and was continued for seven days. At the end of this course the throat culture showed abundant Neisseria species. Beginning Sept. 14, five-tenths gram of streptomycin was administered intramuscularly for seven days. Throat cultures on Sept. 18 and 19 revealed abundant P. aeruginosa. Sensitivity tests revealed the organism to be sensitive to sulfadiazine only in high concentrations, moderately sensitive to terramycin, and not sensitive to streptomycin, aureomycin, or chloramphenicol. On Sept. 19 the patient was presented to a medical-surgical review board, and it was decided that the extensiveness of her disease made surgery inadvisable. The complete blood cell count was normal. Two days later the throat culture showed a moderate number of normal flora plus a moderate number of P. aeruginosa. Beginning on Sept. 26 the patient was treated with tripelennamine (pyribenzamine®) hydrochloride expectorant, 1 dram three times a day for four days. On the day following initiation of this treatment the throat culture showed abundant Neisseria species plus moderate Diplococcus.

During the five-month hospitalization on the Pediatric Service of Fitzsimons Army Hospital the patient had had four bronchoscopic aspirations; postural drainage; vigorous treatment with penicillin, aureomycin, chloramphenicol, streptomycin, and sulfadiazine; potassium iodide, and high-protein high-vitamin diet, but she had shown no improvement. Her weight was 37.5 lb. (17.3 kg.), and her cough continued to be frequent, troublesome, and productive. The cyanosis of the lips and the nailbeds and the clubbing of the fingers was unchanged.

Acetic Acid Aerosol Therapy.—At this time, it was decided to try acetic acid as an antimicrobial agent. On Sept. 28 the patient was placed in a steam tent for 15 minutes three times a day. The liquid in the vaporizer contained 2 tablespoonfuls (1 oz.) of vinegar to 1 liter of water. The patient was discharged from the hospital on Oct. 6 with directions to continue the vinegar-steam inhalations at home. She still showed cyanosis of the lips and the fingernails, with slight clubbing of the fingers. She continued to have paroxysms of coughing. She was seen in the outpatient clinic on Oct. 23 and Nov. 4 with no change in the symptoms or in findings upon physical examination. Throat cultures on these dates showed P. aeruginosa. On Nov. 4 a vitamin-B-complex and iron tonic to be taken daily was prescribed.

The patient was next seen on Dec. 6, at which time she had shown remarkable improvement. The parents stated that she had not coughed at night for a month and that her appetite had improved. She had gained 4 lb. (1.8 kg.). On physical examination the cyanosis of the lips and fingernails and the slight clubbing of the fingers were seen to have disappeared. She was admitted to the hospital for laboratory studies for four days. The chest roentgenogram taken on Dec. 6 was reported as showing clearing of the increased bronchovascular markings and peribronchial pneumonitis that had been seen in April, 1949. Throat cultures taken on Dec. 6, 7, 8, and 9 were negative for P. aeruginosa. However, the throat culture of Dec. 10 showed abundant growth of P. aeruginosa. On Dec. 6 complete blood cell count was normal, and the sedimentation rate was 33 mm. per 60 minutes (Wintrobe). The patient was given acetic acid (1 cc. of 1:1,000 dilution) aerosol three times a day while in the hospital.

In order to note whether the symptoms would return if the acetic acid-steam vapor was withdrawn, this medication was discontinued on Dec. 13.

The patient was seen again on Jan. 10, 1951, and there was no change in the symptoms or results of physical examination. The throat culture showed one colony of P. aeruginosa on this date. Ten days later the patient was seen again, and the parents reported that the nocturnal coughing had been present since Jan. 10. The complete blood cell count on Jan. 20 was normal. The sedimentation rate was 37 mm. per 60 minutes (Wintrobe), and the throat culture showed a moderate growth of P. aeruginosa. The vaporized acetic acid steam inhalations were resumed.

The patient was seen on Feb. 12, and the parents stated that the coughing had subsided since resumption of the acetic acid steam inhalations. The white blood cell count on Feb. 10 was 17,650, with 59% neutrophiles, 34% lymphocytes, and 7% monocytes, and the sedimentation

rate was 26 mm. in 60 minutes (Wintrobe). The throat culture showed abundant P. aeruginosa. This organism was not sensitive to streptomycin, penicillin, aureomycin, chloramphenicol, or terramycin. However, its growth was inhibited in a solution of glacial acetic acid up to a dilution 1 : 8,000 in nutrient broth but did grow in the dilution 1 : 16,000.

The patient was admitted to the hospital again on Feb. 15 for reevaluation. Throat cultures on Feb. 15, 19, 20, and 21 revealed abundant P. aeruginosa, and on Feb. 22 there was normal flora. A bronchoscope was used again on Feb. 16, and viscid purulent material was seen to come from all orifices of the lung but more pronouncedly from the lower lung bronchi. The white blood cell count on Feb. 23 was 20,000, with a normal differential distribution. The patient was discharged on Feb. 23, and the parents were asked to continue the vinegar-steam vapor and to bring the patient back at monthly intervals for outpatient follow-up study. It is contemplated to do bronchoscopy in another six months.

COMMENT

Acetic acid has marked bactericidal effect on the Gram-negative organism P. aeruginosa, and it therefore seemed worth while to try acetic acid aerosol vapor in the treatment of a patient with purulent bronchiectasis, whose respiratory-tract cultures repeatedly showed P. aeruginosa and whose symptoms had not responded to customary antimicrobial therapy. Although the organism persisted, there was a striking decrease in the patient's cough and improvement in her general condition after one month of therapy. Discontinuation of treatment led to a return of the cough, and resumption of treatment resulted in a marked subsidence of this troublesome symptom.

It appears that the marked clinical benefit of an apparently safe and simple method of treatment makes this experience worth reporting. This inexpensive method of treatment can be used in the home for patients with chronic pulmonary suppuration for whom surgical intervention is not suitable.

SUMMARY

A case of chronic purulent bronchiectasis is presented. Upon culture, the predominant causative organism agent was P. aeruginosa. The patient has shown marked clinical improvement when treated with acetic acid aerosol and vinegar-steam vapor, although the presence of the organism has persisted upon culture.

PREMATURE INFANT MORTALITY

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AND
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LOS ANGELES

IN RECENT years much has been done to lower the mortality rate of children. Today fewer children die of infection and other preventable disease than in the past. The rate of deaths due to prematurity has remained high, however, and has not kept pace with the general downward trend in infant death rates. Premature birth is now one of the 10 leading causes of death in the general population.[1]

The Los Angeles County Hospital (Medical Unit) has a bed capacity of 3,794, not including bassinets, and is thus one of the larger hospitals in this country. There are approximately 8,000 live births in the hospital each year. In a hospital of this size a relatively large premature center has been necessary to care for premature infants born in the hospital and also for those referred to the hospital for care. As the interest in premature care has improved, the number of infants cared for has increased.

The Premature Center at the Los Angeles County Hospital (Medical Unit) has at the present time a bed capacity of 92 and an average daily census of 75. Approximately 1,100 infants are cared for in the center each year, and this enables us to present mortality rates on a large series of infants. The center includes nurseries for (1) infants born in the hospital, (2) infants born outside the hospital, (3) suspect cases, (4) isolation, (5) admitting infants, and (6) dismissing infants. Infants born outside the hospital whose weight is above 1,800 gm. (4 lb.) at birth and who are doing well are not transferred to the Premature Center unless the facilities for care at the local hospital are inadequate. All infants are discharged from the hospital when they reach a weight of 2,250 gm. (5 lb.).

A committee of the attending staff, composed of both pediatricians and obstetricians, has been active in finding ways to improve the care of mothers during labor and delivery and of infants following delivery. This committee, with the cooperation of the hospital administration, the School of Nursing, and the local health departments, conducts an advanced course in premature infant care for graduate nurses.

This study was aided by a grant from M & R Laboratories, Columbus, Ohio.

From the Departments of Pediatrics, College of Medical Evangelists, and the Los Angeles County Hospital (Medical Unit).

Paul Johnson, Ph.D., assisted in the statistical evaluation. The assistance of members of the Premature Committee of the pediatric and obstetrical staff in the work of Premature Center is acknowledged.

1. Dunham, E. C.: Premature Infants: A Manual for Physicians, Children's Bureau Publication No. 325, Children's Bureau, Federal Security Agency, 1948, p. 35.

The combined mortality rate for premature infants born in the hospital and for those sent in for care has decreased from 37% in 1941 to 19.5% in 1950. Much of the credit for this must be given to the nursing department for improving the care of infants and to the establishment of a uniform nursing technique.

The accompanying table is a summary of the admissions, deaths, and mortality rates in the Premature Center for the two years 1949 and 1950. All infants who were born alive in the hospital are included. There is an obvious need for standardization of criteria for reporting mortality rates of prematurely born infants. We have included in this series all infants who moved or had heart beat at birth, even though they did not breathe or live long enough to be sent to the nursery. All infants in this series were cared for under a uniform nursery routine, and formulas were given according to the weight of the infant.

From this table it can be seen that the over-all mortality rate is higher for infants born outside of the hospital. Most hospitals with facilities for care of premature

Infants Admitted to Premature Center in Two-Year Period, 1949 to 1950, with Deaths and Mortality Rate by Weight

	1,000 Gm. and Less		1,001-1,500 Gm.		1,501-2,000 Gm.		2,001-2,500 Gm.		Totals	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Admissions										
Born inside	160	..	165	..	386	..	1,012	..	1,723	..
Born outside	54	..	135	..	182	..	95	..	466	..
Total	214	..	300	..	568	..	1,107	..	2,189	..
Discharged alive										
Born inside	14	..	87	..	321	..	979	..	1,431	..
Born outside	6	..	87	..	156	..	80	..	329	..
Total	20	..	174	..	477	..	1,059	..	1,760	..
Deaths										
Born inside	146	91	78	47	35	9	33	3	292	17
Born outside	48	89	48	36	26	14	15	16	137	29
Total	194	90.6	126	42	61	11	48	4	429	19.6

infants do not send an infant to the center for care unless there is a complication or serious illness. This is particularly true of larger infants.

It is not felt that there will be a significant lowering of the mortality rate of infants born in the hospital in the next few years. With better obstetrical care more pregnancies will result in infants born alive rather than in miscarriages. The birth of larger infants will be delayed, and therefore they will not be in the premature weight group. The mortality rate may even increase because of the relatively greater number of smaller babies, with their poorer prognosis.

The following tabulation shows the incidence of premature birth based on birth weight. The incidence is higher than that seen in private obstetrical practice, and

	1949	1950
Total live births in hospital	7,599	8,129
Premature infants	872	851
Per cent premature births	11.5	10.5

it is felt that this higher incidence is due to the lower socioeconomic status and relatively poor nutrition of the mothers admitted to the hospital for delivery. Many patients admitted for delivery have had little, if any, prenatal care; the majority

of them are not conscious of the need for adequate obstetrical care and are unconcerned as to the problems of a premature infant.

Studies of the hospital progress of infants receiving various types of formulas and various caloric intake are being made and will be reported upon later.

SUMMARY

The over-all mortality rate of infants born prematurely at the Los Angeles County Hospital (Medical Unit) for the years 1949 and 1950 was 17%.

With improvement of nursing and medical care of premature infants, the combined mortality rate of both those born in the hospital and those sent in for care has been lowered from 37% in 1941 to 19.5% in 1950.

Of approximately 8,000 live births each year in the hospital, 11% are born prematurely.

312 N. Boyle Ave. (33).

CIRCULATION TIMES IN NEWBORN INFANTS BY THE FLUORESCEIN METHOD

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AND
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DETROIT

RECENT advances in cardiac surgery in infancy have made mandatory an increased knowledge of cardiac physiology in the newborn period. Smith [1] in his book, "Physiology of the Newborn Infant," describes the known changes of circulation in newborn infants but states that additional knowledge would be gained if accurate circulation times were determined for the neonatal period. It would seem reasonable that definitive knowledge in this field may contribute to the understanding of neonatal physiology and to the diagnosis of some forms of congenital heart disease.

Circulation-time studies in newborn infants have utilized various methods and various segments of the cardiovascular system. The inherent technical difficulties are such that considerable discrepancy exists in the small amount of published data.

Feldman [2] calculated that the circulation time equaled 27 times the heart rate. Assuming the average heart rate of a newborn infant to be about 134 beats per minute, he arrived at a circulation time of 12 seconds. Smith [1] cites the work of Haselhorst and Stromberger who injected Congo red dye into the umbilical vein of the pulsating cord and recorded the time interval for the dye to appear in the umbilical artery. They found that in a series of normal births the time was 60 seconds, while in a series delivered by Caesarean section the time was 30 seconds.

Procedures for determination of circulation times which utilize subjective means [3] to determine the end-point are obviously unsuited to newborn infants. Histamine, for which the end-point depends upon flushing of the face,[4] and cyanide, which

From the Children's Hospital, Herman Kiefer Hospital, and Wayne University College of Medicine.

1. Smith, C. A.: Physiology of the Newborn Infant, Springfield, Ill., Charles C Thomas, Publisher, 1945.

2. Feldman, W. M.: Principles of Antenatal and Postnatal Child Physiology, Pure and Applied, London, Longmans Greene & Co., 1920.

3. Averbuck, S., and Friedman, W.: Circulation Times in Normal Children, Am. J. Dis. Child. **49**: 361 (Feb.) 1935. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: Circulation Time in Various Clinical Conditions Determined by Use of Sodium Dehydrochlorate, Am. Heart J. **8**:766, 1933.

4. Robb, G. P., and Weiss, S.: Method of Measurement of Velocity of Pulmonary and Peripheral Venous Blood Flow in Man, Am. Heart J. **8**:650, 1933.

depends upon respiratory changes, are highly impractical in a flushed, hyperpneic, excited infant. Hubbard and his associates [5] measured in older children the interval from the time of injection of radioactive sodium into a vein of one arm until radioactivity was noted by a Geiger counter placed over the opposite hand.

With the advent of a nontoxic fluorescent substance, fluorescein [6] and the availability of an adequate Wood's light (long-wave ultraviolet light),[7] a way became available for this study, and only the technical difficulties of intravenous work in newborn infants became a barrier. Lange and Boyd [8] have utilized fluorescein, and a few accounts [9] have appeared in the literature since that time. Witzberger and Cohen [10] have found normal circulation times of 6 to 9 seconds, arm-to-lips, in children 3 months to 1 year old. Slobody and his associates [11] reported a study of 90 newborn infants in whom the umbilical-vein-to-lip or ductus-venosus-to-lip circulation time was determined within the first two hours of life by the fluorescein technic. In the first 45 infants the mean umbilical-vein-to-lip time was 4.8 ± 0.6 seconds, with a range of 3.3 to 5.8 seconds.

Frequently in clinical work the question of circulation times of an infant is raised after the first few hours of life, at a time when the umbilical-vein technic is unavailable for accurate circulation-time determinations. At such times a study of the peripheral-circulation times, e. g., arm-to-conjunctivae, is necessary, and a knowledge of the normal peripheral circulation of newborn infants is essential for comparison. For this reason the following clinical method was utilized.

MATERIALS AND METHOD

The circulation times of 55 normal newborn infants were determined. The infants were selected at random from the newborn nursery at the Herman Kiefer Hospital, Detroit. The infants varied in age from 30 minutes to 9 days and in size from 5 lb., 5 oz. (2,400 gm.) to 9 lb. 7 oz. (4,300 gm.). In all cases the babies were delivered by spinal anesthesia. All deliveries were uncomplicated, and in all cases the cord was not tied until pulsations had ceased.

A No. 23 to 25 needle was introduced into a vein on the dorsum of the hand or the ventral surface of the wrist. The tourniquet was loosened, the room light extinguished, and, at a signal, 0.07 cc. per pound (0.5 kg.) of body weight of a solution containing 5% sodium fluorescein and 5% sodium bicarbonate ("fluorescite") was quickly injected. A stop watch was used to measure the time from the initial injection until a bright green fluorescence was noted on the palpebral conjunctivae when viewed under Wood's light.

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5. Hubbard, J. P.; Preston, W., and Ross, R.: Velocity of Blood Flow in Infants and Young Children Determined by Radioactive Sodium, J. Clin. Invest. **21**:613, 1942.

6. The fluorescein used in this study was "fluorescite," 10-cc. ampoules, C. F. Kirk Co., New York.

7. The Wood's light used was a Hanovia Wood's Lamp, Type 16106, 115 volts, 60 cycles, Hanovia Chemical & Manufacturing Company, Newark, N. J.

8. Lange, K., and Boyd, L. J.: Use of Fluorescein in Determining Adequacy of Circulation, M. Clin. North America **26**:943, 1942.

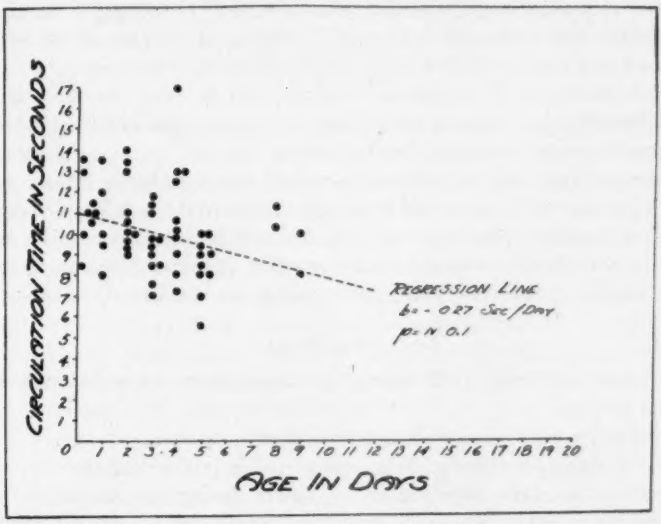
9. Gasul, B. M.; Marino, J. J., and Christian, J. R.: Fluorescein Circulation Time in Normal and Pathologic Conditions in Infants and Children, Including Various Types of Congenital Malformations of the Heart, J. Pediat. **34**:460, 1949. Seckel, H.: Blood Volume and Circulation Time in Children, Arch. Dis. Childhood **11**:21, 1936.

10. Witzberger, C. M., and Cohen, H. G.: Circulation Time in Infants and Young Children Determined by the Fluorescein Method, J. Pediat. **22**:726, 1943.

11. Slobody, L. G.; Rook, G. D.; Levbarg, M., and Morcey, M.: Studies of the Cardiovascular and Renal Systems in the Newly Born Infant Using Fluorescein: I. Circulation Time Immediately after Birth, Pediatrics **6**:254, 1950.

RESULTS

The accompanying illustration is a scatter chart of the results of the hand- or wrist-to-conjunctivae-circulation times by the fluorescein method in 55 newborn infants. The average circulation time for the first five days of life was 10.2 seconds, with the 95% range including ± 4.2 seconds. The results in the first day of life in our group ranged from 8.5 to 13.5 seconds; however, determinations for this one day were insufficient to note a significant 95% range. From the first to the fifth day there appeared to be a trend toward reduction of the circulation time, but statistical determination of regression showed only questionable significance of this observation.



Results of hand- or wrist-to-conjunctivae-circulation times by fluorescein method in 55 newborn infants.

COMMENT

The literature reveals very few determinations of the circulation times of newborn infants. The one exception is the report of Slobody and his associates [11] on infants less than 2 hours old. Our series used arm-to-conjunctivae circulation instead of umbilical-vein-to-lip so that we would have a method available for clinical use after the first day of life and one which we could compare with the results of Witzberger and Cohen for the slightly older age group. It is, therefore, not suprising that our results are somewhat at variance. In our experience the conjunctivae gave a sharper end-point than did the lip.

A number of factors influence the velocity of circulating blood, such as blood volume, blood pressure, blood viscosity, pulse rate, and cardiac size.[12] The maturation of circulation in newborn infants includes the closure of the ductus arteriosus and intracardiac shunts, as well as establishment of a pulmonary circulation. The velocity of a complete circulation also depends upon the timing of these changes in

12. Nathanson, M. J., and Eleck, S. R.: Influence of Heart Size on Circulation Time, Am. Heart J. **33**:464, 1947.

the neonatal period. Differences in technic, such as the particular vein selected or the size of the needle used, may also give rise to variance in results.

In our series there was no correlation in color, sex, weight, or height. Determinations on a few premature infants, while too few as yet to be conclusive, suggest a greater correlation with the age of the patient than with the size of the infant or the degree of prematurity.

Three abnormal newborn patients with suspected congenital heart disease have since had circulation times determined by this method. The first infant showed a 2½-second circulation, wrist-to-conjunctivae, and at autopsy subsequently proved to have a complete transposition of the great vessels. A second infant with sclerema was within the normal range, with a circulation time of 13 seconds at one day of life. A third infant with a circulation time of 17 seconds at 4 weeks of life had cardiac failure confirmed shortly thereafter and responded to digitalis therapy.

The determination of circulation times appears to offer one more aid in the better understanding of neonatal physiology and another clinical tool in the diagnosis and differentiation of congenital heart diseases.

For the guidance of those who may set up this technic in the future, we should perhaps point out that it was found necessary to discard the first 20 to 25 determinations before dependable and accurate results could be obtained consistently. The reason for this is the necessity to train the team for close coordination and to acquire sufficient familiarity with the end-point essential for consistently accurate results.

CONCLUSIONS

The circulation times of 55 normal newborn infants were determined by the fluorescein method.

The method used is readily adapted for clinical purposes.

The 95% range for the 0-to-5-day age period is 10.2 ± 4.2 seconds.

The circulation time appeared to be slower during the immediate postnatal period and appeared to accelerate gradually during the subsequent five days of observation. The regression was —0.27 seconds per day, but this may prove insignificant.

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The statistical analysis of case material by Dr. Park Gerald, Department of Pediatrics, Michael Reese Hospital, is acknowledged. Dr. B. M. Kagan, Chairman, Department of Pediatrics, Michael Reese Hospital, and Dr. Paul V. Woolley Jr., Medical Director, Children's Hospital, Detroit, gave comments and advice in the preparation of this paper.

EXTREME EOSINOPHILIA, INCREASED BLOOD HETEROPHILE-AGGLUTINATION TITER, AND HYPERGLOBULINEMIA

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PERSISTENT and marked eosinophilia of the blood is found in a variety of conditions, including parasitic infections, various skin diseases, allergic conditions, periarteritis nodosa, dermatomyositis, erythema multiforme, leukemia, Hodgkin's disease, rheumatoid arthritis, and convalescence after various infectious diseases; but there still remain isolated cases in which extreme eosinophilia occurs but which do not seem to fit any of the above categories. These have been classified as extreme eosinophilia and leucocytosis,[1] eosinophilia with splenomegaly,[2] chronic eosinophilia,[3] Löffler's syndrome,[4] eosinophilia leucemoides,[5] and familial eosinophilia.[6] However, it would appear that they may all be part of a clinical entity which was recently described by Zuelzer and Apt [7] under the title "Disseminated Visceral Lesions Associated with Extreme Eosinophilia."

The purpose of this paper is to present the case of a 27-month-old child in which there were many of the clinical and laboratory findings described by Zuelzer and Apt but with the additional finding of a marked and persistent elevation of the routine heterophile-agglutination titer which could be eliminated by absorption with guinea-pig kidney or with boiled-beef red blood cells.

From the Division of Pediatrics, University of California School of Medicine.

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6. Atmar, R. C.: Familial Eosinophilia: Report of Case with Biopsy of Liver, J. A. M. A. **115**:449 (Aug. 10) 1940.

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REPORT OF A CASE

J. D., a 27-month-old white boy, entered the University of California Hospital on July 12, 1941, because of lymph adenopathy, known eosinophilia of six months' duration, and repeated febrile episodes during the preceding year.

He was well until the age of 10 months, when a temperature of 104.6 F. developed, without prodrome or associated malaise. The family physician made a diagnosis of tonsilitis and administered two injections of penicillin. Moderate cervical adenopathy was said to be present at the time. The findings from a study of the blood were "normal," with lymphocytes constituting 42% of the white blood cell count. The fever and adenopathy cleared in one week.

Ten months later, having been symptom-free in the interim, the child had another similar attack, with cervical adenopathy and temperature of 104 F. However, strikingly abnormal findings were reported from a study of the blood, the white cell count being 25,000 per cubic millimeter, with an eosinophilia of 45%. Follow-up study of the blood three months later, during a symptom-free period, revealed a white cell count of 36,000 per cubic millimeter, with a 41% eosinophilia.

Five months after the second attack, the temperature rose to 102.6 F., and cervical adenopathy was the only significant physical finding noted. Penicillin was again administered by injection, and the patient was referred to the University of California Hospital for study.

TABLE 1.—*Laboratory Data on*

Date	Time After Hospital Admission	Hemoglobin, Gm.	Red Blood Cells, Millions	Packed Red Blood Cells, Cc./100 Cc.	White Blood Cells, No.	Eosinophile Count, %	Uncorrected Sedimentation Rate	Serum Protein		
								Total, Gm.	Albumin, Gm.	Globulin, Gm.
7/12/49	Entry*	12.5	4.2	33	32,000	58	34	...	...	...
7/18/49	5 days	11.0	4.36	..	41,000	59	..	...	...	...
8/17/49	1 mo.	11.5	4.75	35	42,300	65	39	9.7	4.5	5.2
9/28/49	2 mo.	12	4.49	..	27,800	63	..	...	...	...
11/23/49	4 mo.	10	4.3	..	28,700	55	..	5.6	3.0	2.6
3/15/50	8 mo.	11.5	4.6	..	16,600	34	..	...	...	...
7/26/50	12 mo.	11.5	4.1	..	10,800	26	..	6.7	4.9	1.8
4/10/51	21 mo.	12	4.3	..	11,000	12	..	6.9	3.9	3.0

* The following data were also elicited upon entry. There was no evidence of eosinophilia in the child's maternal grandmother, mother, father, and two siblings. The patient's platelet count was normal, bleeding time was 3 min., and clotting time was 7 min. Bone marrow aspiration contained 53% eosinophiles, with 26% mature forms. Blood-agglutination reactions were negative for typhoid, paratyphoid A and B, brucellosis, and tularemia, and the stools contained no ova or parasites. A chest roentgenogram and the results of urinalysis were normal. Skin tests with tuberculin, coccidioidin, Trichinella, and Echinococcus elicited negative reactions.

† Doubtful reaction.

At no time in the course of these attacks had weakness, fatigue, weight loss, anorexia, bowel disturbance, cough, abdominal pain, or a bleeding tendency been noted. The child had a history of ingestion of unpasteurized milk, but no history of ingestion of undercooked pork or other meats.

The family history revealed the presence of "glandular disease" in the maternal grandfather and aunt, both living (and apparently well) in Denmark. On the paternal side, the grandmother died of pulmonary tuberculosis and the father and two uncles also had had active forms of the disease. This child had no known contact with these relatives except the father, in whom the disease had been arrested prior to the patient's birth. There was no family history of allergy.

The past history was essentially noncontributory. The patient was born in California and had never been out of the state. He was delivered at term following an uncomplicated pregnancy, weighing 7 lb. (3,200 gm.). Development was normal in all respects. The only recognized diseases were epidemic parotitis and measles.

Significant physical findings on entry were limited to the abdomen, where the liver was found palpable 2 cm. below the right costal margin, and the tip of the spleen was felt below the left costal margin; on all subsequent examinations, however, the latter was not palpable. No abnormal adenopathy was present, though small, discrete, movable nodes could be felt in the cervical, axillary, and inguinal regions.

Laboratory data are listed in Table 1. The initial blood count showed leucocytosis and a 58% eosinophilia. Eosinophilia persisted for the subsequent 21 months, while leucocytosis continued for almost a year.

Blood smears of the maternal grandmother, mother, father, and two siblings were studied, but no eosinophilia or other abnormal findings were noted. The bone marrow had 53% eosinophiles, 26% of which were mature cells, but was otherwise normal. Upon entry the routine heterophile antibody titer was positive at 1:112, plus-minus at 1:224, and negative at 1:448. The titer was still elevated 21 months later. Serum proteins were found to total 9.7 gm. per 100 cc., albumin constituting 4.5 gm. and globulin 5.2 gm.

One month after hospitalization the routine heterophile titer was positive at 1:112 and negative at 1:242. Serum absorbed with guinea-pig kidney was negative at all dilutions, while serum absorbed with boiled-beef red blood cells was positive at 1:14 and negative at 1:28. Several subsequent tests revealed similar results (Table 1). Hyperglobulinemia was still present 21 months after entry to the hospital.

Results of roentgenologic examination of the chest were reported normal. A nasal smear was found to contain a moderate number of eosinophiles.

A diagnosis of visceral eosinophilia was made. No treatment was given, and the patient had an afebrile and uncomplicated stay in the hospital.

Twenty-Seven-Month-Old Child

Antibody Study, Routine Heterophile, Titer							Serum Absorbed with Guinea-Pig Kidney	Serum Absorbed with Boiled-Beef Cells, Dilution				Kolmer Reaction	Kahn Reaction	Eosinophiles in Nasal Smears
1:28	1:56	1:112	1:224	1:448	1:896	1:1,292		1:14	1:28	1:56	1:112			
+	+	+	±	−	−	−	..	..	..	..	..	..	..	.....
+	+	+	+	±	±	−	..	..	..	..	..	..	..	.....
+	+	+	−	−	−	−	−	+	−	..	..	..	..	.....
+	+	+	±	−	−	−	−	+	±	±	−	..	..	.....
+	+	+	+	±	−	..	..	+	±	±	−	−	††	None
..	..	..	..	..	..	..	..	..	..	..	..	..	..	Moderate no.
+	+	±	−	−	−	−	..	+	±	−	..	.	..	Many
+	±	−	−	−	−	−	..	..	..	..	..	−	−	Scattered

The child was followed in the University of California Hematology Clinic, where it was reported that he had slight elevations of temperature (to 99.5 or 100 F.) almost biweekly. He had repeated colds, and between these infections a thin nasal discharge and sneezing were noted. The liver and spleen were no longer palpable.

He was seen in the clinic at frequent intervals for the following 18 months. He continued to have frequent upper respiratory infections, but the mother reported that he no longer had fever, nasal discharge, or sneezing between attacks.

COMMENT

Zuelzer and Apt described a series of eight cases of young children, ranging in age from 18 months to 3 years, who presented variable clinical pictures but in whom eosinophilia of the blood and bone marrow, hyperleucocytosis, and hyperglobulinemia persisted over long periods. The clinical manifestations included hepatomegaly, pulmonary infiltrations, asthmatic complaints, joint symptoms, urticaria, and convulsions. However, the patients were free of symptoms during much of their course. Microscopic examination was made of the pathologic lesions of the liver in four cases, and the lesions were found to consist of necrosis, granuloma formation, and severe eosinophilic infiltrations in the lungs of patients, which corresponded to those described by other authors with the so-called Löffler syndrome.

Zuelzer and Apt concluded that in all of these cases there was a common pathologic process of variable localization and severity, the nature of which they regarded as an allergic-hyperergic tissue response to undetermined antigens. In contrast to the picture of Löffler's syndrome in adults, in whom eosinophilia and leucocytosis are usually of moderate degree with predominantly pulmonary localization, the process in young children was found to affect the liver to a greater degree, and hyperleucocytosis appeared to be more frequent and more marked in children than in adults with this condition.

No biopsy was done of the liver or other tissues in our patient, but there was transitory enlargement of an organ in the left upper quadrant of the abdomen, which suggested that the spleen or left lobe of the liver had been involved in the disease process. Involvement of the liver in cases of extreme and persistent eosinophilia has been described by Atmar [6] and by Perlingiero and György,[3] and the latter authors believe the condition to be due to an allergic response to Ascaris infection. Splenic enlargement has been described mainly in children. It has been suggested that the presumed splenic enlargement might actually have been due to a greatly enlarged left lobe of the liver. Because of the very transitory and mild degree of

TABLE 2.—*Comparative Data on Absorption of Antibodies*

	Agglutinins Absorbed	
	Guinea-Pig Tissue	Beef R. B. C.
Normal sera	+	0*
Infectious mononucleosis	0†	+
Serum sickness	+	+
Patient, J. D.	+	+

* One-third absorbed.
† One-half to three-fourth absorbed.

enlargement of an organ in the left upper quadrant of the abdomen in our patient, it was difficult for us to be certain that it was actually an enlarged spleen.

It has been assumed that the basis of the condition is an allergic-hyperergic reaction, because of the occurrence of such allergic manifestations as asthma, urticaria, and pulmonary infiltrations in other patients. However, none of these had ever been present in our patient, nor was there any known familial predisposition to any allergic manifestation. Instead he demonstrated clinical findings (pharyngeal injection, transient cervical adenitis, and fever) which are common in many upper respiratory infections.

Changes in the blood cell count were limited almost exclusively to leucocytosis with a marked elevation of the eosinophilic leucocytes. The eosinophiles were mature. Anemia and thrombocytopenia did not appear to be a part of the picture. The bone marrow showed a marked increase in eosinophilic elements, with 53% of the cells being of this series.

Hyperglobulinemia, which may not be as persistent as the eosinophilia, is of particular interest and was found in the patient of Perlingiero and György, in four of Zuelzer and Apt's patients, and in our patient.

Significantly elevated levels of heterophile antibodies (antisheep agglutinins) were found by the usual method of testing. However, the antibodies were absorbed by guinea-pig tissue (kidney emulsion) and boiled-beef red blood corpuscles. These

findings differ from those found in infectious mononucleosis (Table 2) and are similar to those noted in serum sickness. Only random observations of the heterophile agglutination titer have been made in the other cases reported in the literature. In two of Zuelzer and Apt's cases, it was reported as being positive at 1 : 112 and 1 : 56, respectively, while in a third it was negative. No mention is made of the effect of absorbing the agglutinins with guinea-pig tissue or with boiled-beef red blood cells.

As an etiologic factor, sensitivity of our patient to bacterial products or to penicillin was considered. Since the child had received two injections of penicillin at a time when no eosinophilia of the blood was present, sensitivity to this drug cannot be excluded. However, the fact that eosinophilia persisted for months following penicillin administration and that it was not administered in other cases (most of which were described prior to the widespread use of antibiotics) does not permit us to make any conclusions as to the specific etiologic agent.

The prognosis in general is good, although 2 of the 10 children described in the reports collected by Selander [5] died, and one child in Zuelzer and Apt's series died. However, in these patients it could not be stated categorically that the disease entity under discussion was the immediate cause of death. One of Bass's patients died following whooping cough and bronchopneumonia, and an autopsy was not performed.

Our patient continues to be in good health two years after the eosinophilia was first noted, but there is some evidence that the disease process is still active.

CONCLUSIONS

A case of persistent marked eosinophilia of the blood, associated with hyperglobulinemia and increased blood heterophile agglutination titer, in a 27-month-old child is presented.

Differential agglutination with guinea-pig emulsion and boiled-beef red blood corpuscles showed that the heterophile antibodies were similar to those found in serum sickness.

Case Reports

CONGENITAL DIRECT COMMUNICATION BETWEEN BILIARY SYSTEM AND RESPIRATORY TRACT

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WE ARE reporting this case of tracheocholedochal tract as an instance of a developmental anomaly with which we are not acquainted, either from our own previous experience or from a survey of the literature. Yellow discoloration of the sputum along with a positive chemical reaction for the presence of bile proved to be the leads to the diagnosis which was established indubitably by roentgenologic examination. Had the diagnosis been made sooner, surgical correction of this anomaly might well have been effected.

REPORT OF A CASE

J. N., a 5-month-old girl, was admitted to the Children's Medical Center Feb. 4, 1949, because of persistent respiratory difficulty.

The pregnancy had been uncomplicated and had gone to full term, with a normal low forceps delivery after six hours of labor. Birth weight was 5 lb. 14 oz. (2,660 gm.). The father, age 32, and the mother, age 30, were in good health, as was one sibling, an 18-month-old brother.

The patient had no observable difficulty until four days after birth, when she vomited and became feverish (temperature, 105 F.). A clinical diagnosis of atelectasis or pneumonitis was made, and improvement was associated with penicillin treatment. The infant was discharged from the maternity hospital at the age of 24 days, apparently doing satisfactorily. Four days later she began to cough up large amounts of green mucoid material and on one occasion became cyanotic.

She was rehospitalized, and a diagnosis of right lower lobe atelectasis was made. The cultured sputum showed Pseudomonas aeruginosa and hemolytic Staphylococcus aureus. Bronchoscopic removal of a mucous plug from the right bronchus was followed by reexpansion of the atelectatic lobe. In spite of administration of penicillin, streptomycin, various sulfonamides, and oxygen therapy, she continued to vomit, and her stools became loose, watery, and foul. The sputum was yellow to bright orange.

At 7 weeks she was transferred to another hospital, where the sputum continued to be copious and orange. The abdomen was slightly distended. Despite therapy with aureomycin, dihydrostreptomycin, polymyxin, and sulfadiazine, she did poorly; Ps. aeruginosa was constantly cultured from the sputum. Roentgenologic studies revealed intermittent atelectasis of the right middle lobe and on one occasion of the right lower lobe and the left lower lobe; there were associated areas of pneumonitis. Bronchoscopy on two separate occasions revealed normal-appearing trachea and main bronchi, although the examination was hindered by the abundant sputum. She continued to vomit and cough up thick yellow material, especially after feeding.

She was admitted to the Children's Medical Center at 5 months, weighing 7 lb. 13 oz. (3,440 gm.). She appeared chronically ill and moderately cyanotic, with coarse rhonchi throughout each lung. She produced a profuse, sticky, yellow mucoid sputum which accumulated in the posterior pharynx, necessitating frequent aspirations.

From the Departments of Radiology and Pathology, Harvard Medical School, and the Children's Medical Center.

Urinalysis showed no abnormalities. The red cell count was 4,000,000; hemoglobin, 13.0 gm. per 100 cc.; white cell count, 13,700, with 51% polymorphonuclear leucocytes, 41% lymphocytes, 7% monocytes, and 1% eosinophiles. Nonprotein nitrogen was 39 mg. per 100 cc.; serum protein, 6.0 gm. per 100 cc. Serological test for syphilis gave a negative result, as did a 1:500 dilution tuberculin skin test. Numerous nose and throat cultures showed Escherichia coli and Ps. aeruginosa. Liver function tests showed evidence of hepatic damage: thymol turbidity, 7.5 units; thymol flocculation, 3+; cephalin-cholesterol flocculation, 3+; colloidal gold, 4+; free serum bilirubin, 0.19 mg. per 100 cc.; total serum bilirubin, 0.31 mg. per 100 cc.

The diagnosis of pancreatic insufficiency was entertained, but trypsin activity was present in the duodenal juice as well as in the stools.

Roentgenographic examination of the chest (Fig. 1) showed atelectasis of the major portion of the right middle lobe, as well as small scattered atelectatic areas on the left, with several regions of compensatory emphysema. In addition, there were mottled areas of increased density

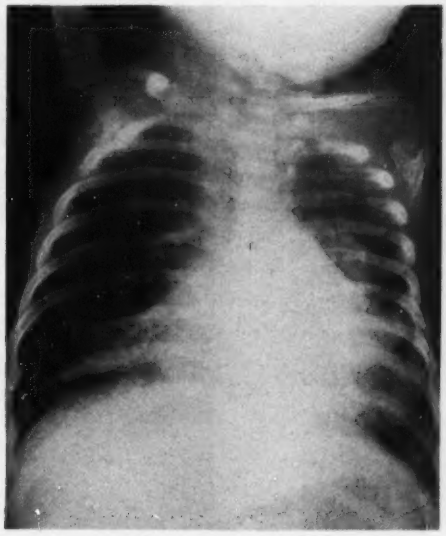

Fig. 1.—Chest roentgenogram taken on admission.

throughout both lung fields, suggesting a superimposed diffuse pulmonary infection. The heart appeared enlarged and the intrapulmonary vessels increased in caliber.

The patient was treated with oxygen, and the upper respiratory tract was suctioned frequently of yellow, frothy fluid.

Reexamination of the chest on the fifth hospital day again showed the atelectasis of the middle lobe and also segmental collapse of the lower lobe on the right, with compensatory emphysema of the upper lobe. On the left there was also extensive atelectasis of the lower lobe with moderate shift of the heart and mediastinum to the left.

On the 12th hospital day fluoroscopic examination showed the appearance of the lungs to vary dramatically during the course of the examination. There was persistent collapse of the right middle and lower lobes, with compensatory and partially obstructive emphysema of the right upper lobe. On the left there was at one moment complete obstructive emphysema of the entire lung, a few moments later total atelectasis, and at another time atelectasis of the lower lobe with reexpansion of the upper lobe. These changes varied with the amount of secretions in the trachea and bronchi. Iodized oil swallow and then barium swallow showed no abnormality of the esophagus and no evidence of a fistulous communication with the trachea.

Because of the persistence of the yellow frothy upper respiratory tract secretions, an anomalous connection between the respiratory tract and the biliary system was considered, and tests of sputum on two separate occasions did indicate the presence of bile (positive Gmelin and positive iodine ring reactions). The pH of these secretions was alkaline (over 7.5). In an attempt to demonstrate the anomaly, fluoroscopic examination of the chest was done during the instillation of about 30 cc. of iodized oil into the trachea. The bronchial tree showed extensive fusiform dilatation generally. An abnormal tract was readily demonstrated, arising from the medial aspect of the right main bronchus just below the carina tracheae and extending directly downward through the mediastinum parallel to and anterior to the esophagus.

At the level of the diaphragm this tract coursed laterally toward the right and appeared to pass through the shadow of the liver to enter the duodenum about at the level of the ampulla (Fig. 2). The upper portion of the tract appeared somewhat smaller in diameter than the main stem bronchi. It was thus established that there was a patent, direct communication between the right main stem bronchus and the duodenum, possibly by way of the biliary duct system.

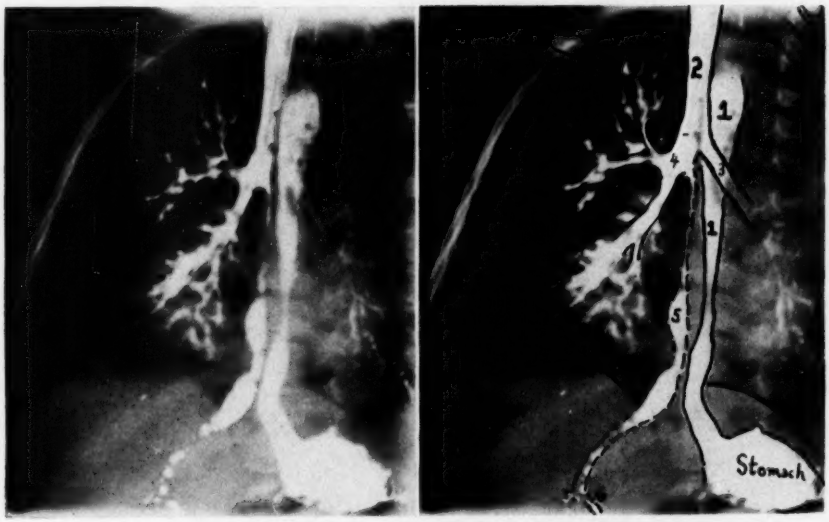

Fig. 2.—Instillation of iodized oil through a tracheal catheter. During the procedure the patient coughed up and then swallowed a good deal of the material; thus the esophagus and stomach contained iodized oil: (*1*) esophagus, (*2*) trachea, (*3*) left main bronchus, (*4*) right main bronchus, (*5*) anomalous tract, (*6*) biliary system, including the common bile duct coursing toward the duodenum.

Preparations were made for surgical exploration with intent to ligate the tract as a first step to interrupt the flooding of the lungs with bile and possibly duodenal juice, but before the operation could be started, the infant suddenly became extremely cyanotic and died, apparently from massive airway obstruction.

Gross Examination.—The body was that of a fairly well developed but poorly nourished white girl measuring 58 cm. in length (normal 62 cm.). There was no icterus, cyanosis, or edema, and the external examination showed no abnormalities other than a liver palpable 3 cm. below the right costal margin.

The abdominal cavity contained 20 cc. of clear fluid; the various organs had normal positions. The gall bladder was normal in size and extended 0.5 cm. below the liver edge.

Each thoracic cavity contained 10 cc. of clear fluid. Both the upper lobes and the right middle lobe were hyperexpanded, and both lower lobes were collapsed.

The mediastinum was displaced to the left. The pericardium and heart were normal. Joining the right main bronchus immediately to the right of the carina tracheae was an anomalous tract,

0.7 cm. in diameter, bordered by cartilage rings for the upper 2 cm., and filled with bile-stained mucopurulent material. This tract ran in the posterior mediastinum parallel with and to the right of the esophagus; it passed through the esophageal hiatus of the diaphragm, where it turned to the right behind the left lobe of the liver to become continuous with the hepatic duct (Fig. 3). Three large hepatic branches and the cystic duct joined the hepatic duct. The common duct had the usual course and was not abnormal in size. The tract was easily dissected free for its entire length and showed no evidences of inflammatory adhesion to the surrounding structures.

The heart weighed 30 gm. (normal 30 gm.) and showed no gross abnormalities. The right lung weighed 75 gm. (normal 42 gm.) and the left 60 gm. (normal 39 gm.). Both upper lobes

Fig. 3.—Viscera, showing opened trachea with anomalous tract running parallel to esophagus and joining hepatic duct. The upper probe runs from the trachea down the tract to the common duct; the lower probe is inserted through the wall of the common duct to the duodenum: (*1*) trachea, (*2*) left main bronchus, (*3*) right main bronchus, (*4*) esophagus, (*5*) anomalous tract, (*6*) gall bladder, (*7*) pancreas, (*8*) common duct, (*9*) duodenum.

and the right middle lobe were emphysematous, with a few atelectatic foci visible on section; both lower lobes were dark red and firm. The bronchioles were unusually prominent in all areas of the lungs. The right main and both upper lobe bronchi were partially filled with thick yellow-green mucopurulent material; the right middle and both lower lobe bronchi were completely filled. Smears of this material showed many Gram-positive cocci and polymorphonuclear leucocytes. The result of Gmelin's test for bile was equivocal. Culture of material from the right lower lobe showed Ps. aeruginosa. The trachea contained a large amount of similar material, and its mucosa was thick and reddened. The hilar nodes were enlarged.

The spleen was normal. The esophagus showed many mucosal petechiae near the cardia. The stomach contained bile-stained fluid. The small intestine was normal; the ampulla of Vater was normally situated and patent to probing.

The liver weighed 138 gm. (normal 200 gm.), was firm and red-brown, and showed no gross evidence of inflammation. The gall bladder was normal in size and shape and contained pale, moderately viscid bile. The right kidney weighed 18 gm. (normal 26 gm.) and the left 21 gm. (normal 25 gm.); neither showed any abnormality externally or on cut surface. The pancreas, adrenals, ureters, bladder, vagina, uterus, tubes, ovaries, aorta, vena cava, portal vein, tongue, and larynx presented no abnormalities; the ribs and vertebrae appeared normal on section. The brain weighed 512 gm. (normal 660 gm.) and was normal grossly.

Microscopic Examination.—Routine sections of the heart, esophagus, stomach, small intestine, colon, pancreas, kidneys, adrenals, ovaries, Fallopian tubes, bladder, diaphragm, aorta, skin, cerebral cortex, basal ganglia, cerebellum, pons, medulla, and spinal cord showed no significant abnormalities.

The lungs had areas of atelectasis and emphysema. The bronchi and bronchioles were generally filled with mucopurulent exudate; the peribronchial and peribronchiolar tissues were thickened and infiltrated with mononuclear cells. There was diffuse acute and chronic pneumonitis.

The alveoli contained large numbers of neutrophiles, lipophages, and rare phagocytes containing small golden granules suggesting bile pigment. The hilar nodes showed reticulum cell hyperplasia and diffuse polymorphonuclear infiltration. The spleen was congested, and the Malpighian bodies were small. The liver was moderately edematous, but there were no evidences of inflammation, bile stasis, or fatty metamorphosis. The trachea and tongue showed mild chronic subepithelial inflammation. The ribs bore minimal manifestations of growth disturbance. The fat depots of the skin, mediastinum, and abdomen showed marked depletion.

Sections of the upper 2 cm. of the tracheocholedochal tract showed a stratified squamous, noncornified epithelium surrounded by small irregular cartilage masses and many serous and mucinous glands which interrupted poorly formed inner circular and outer longitudinal muscle layers. The remainder of the mediastinal portion of the tract had a similar epithelium and smaller numbers of glands of the same type; in this region a definite muscularis mucosae as well as inner circular and outer longitudinal muscle layers could be made out. In its abdominal portion the tract was lined by pyknotic simple pseudostratified or stratified columnar epithelium which was absent in many areas, probably as the result of probing. The wall consisted of collagen fibers with no muscle bundles and contained a few small simple mucous glands. Mild chronic inflammation of the mucosa was present at all levels. The upper 2 cm. of the tract thus resembled larynx most closely; the rest of the thoracic portion, esophagus, and the abdominal portion, bile duct.

Very likely the inflammatory changes in the upper respiratory tract were due primarily to irritation caused by the upward passage of bile into the trachea and then to the lungs, leading to a chemical and later a bacterial pneumonitis.

PATHOGENESIS

At least two possible mechanisms of development of this congenital anomaly suggest themselves. The first, favored by Dr. G. L. Bremer,[1] is that the tract resulted from union of an anomalous bronchial bud with an anomalous bile duct. The trachea and bronchi develop as ventral buds from the entodermal tube in embryos of 4 to 7 mm. The bronchial anlages continue to branch in such a way that the stem bud is retained as the main bronchial element, i. e., at first the branching is monopodial, not dichotomous, lateral buds being given off from the stem bud proximal to its growing tip.[2] Anomalous bronchi may occur and may enter or extend through the

1. Bremer, J. L.: Personal communication to the authors.

2. Arey, L. B.: Developmental Anatomy: A Text-Book and Laboratory Manual of Embryology, Philadelphia, W. B. Saunders Company, 1924, P. 114.

diaphragm.[3] At about the same stage of development of the embryo, the hepatic diverticulum is formed as a ventral outgrowth from the fore-gut. The hepatic diverticulum gives rise to the glandular portion of the liver and itself differentiates into the gall bladder and the large biliary ducts. One might suppose that an anomalous biliary duct extending cephalad could join with an accessory bronchus coursing caudad to give rise to a tracheocholedochal tract.

The fact that the upper portion of the anomalous tract in our patient was ringed by cartilage similar to that of a bronchus gives support to this concept.

The second mechanism which occurs to us is that the tract represented a duplication of the upper gastrointestinal tract for the distance of the gut between the laryngotracheal outgrowth and the hepatic diverticulum. Support to this concept is afforded by the fact that the major portion of the tract histologically resembled esophagus rather than bronchus or bile duct.

Which of these explanations, if either, is correct cannot be established at present.

SUMMARY

The congenital communicating tract between the trachea and right main bronchus reported in this paper as occurring in an infant is unusual. The abnormality was roentgenologically demonstrable. Histologic examination of the tract showed that the upper portion resembled trachea; the middle, esophagus, and the lower, bile duct.

3. Bremer, J. L.: Accessory Bronchi in Embryos: Their Occurrence and Probable Fate, Anat. Rec. **54**:361 (Nov. 25) 1932.

RECTAL LESIONS OF LYMPHOGRANULOMA VENEREUM IN CHILDHOOD

Review of the Literature and Report of a Case in a Ten-Year-Old Boy with Rectal Stricture

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LYMPHOGRANULOMA venereum is generally considered a disease of adult life and its occurrence in childhood a rarity. A review of the literature bears this out. Therefore, this case of a 10-year-old boy with a rectal stricture due to lymphogranuloma venereum seems to merit reporting.

Lymphogranuloma venereum is an infectious disease caused by a virus and usually transmitted by venereal contact. It is a systemic disease with many varied local manifestations, which include inguinal adenitis, esthiomene (elephantiasis of the vulva), urethritis, conjunctivitis, and the anorectal syndrome of proctitis and

Cases of Rectal Lesions Due to Lymphogranuloma Venereum in Children

Case No.	Source	Date Reported	Age, Yr.	Sex	Inguinal Adenitis	Rectal Lesion	Frei Reaction
1	Elitzak and Kornblith [1a]	1935	8	F	..	+	+
2	Dick [1b]	1936	14	F	..	+	+
3	Banciu and Caratzali [1c]	1938	11	M	+	+	+
4	Sonck [1d]	1939	8	F	..	+	+
5	Sonck [1d]	1939	4	F	+	+	+
6	Sonck [1d]	1939	5	F	..	+	+
7	Sonck [1d]	1939	5	F	..	+	+
8	Sonck [1d]	1939	6	F	..	+	+
9	Gulowsen [1e]	1939	9	F	+	+	+
10	Sonck [1f]	1940	2	F	+	+	+
11	Winge [1g]	1941	6	F	+	+	+
12	Winge [1g]	1941	16	F	..	+	+
13	Banov	1952	10	M	..	+	+

stricture formation. No one symptom is pathognomonic of the disease. The diagnosis is suggested by the clinical picture and confirmed by the Frei test and/or the complement-fixation reaction.

A synopsis of previously reported cases [1] of rectal manifestations of lymphogranuloma venereum in children in the world literature is presented in the accom-

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1. (*a*) Elitzak, J., and Kornblith, B. A.: Lymphogranuloma Inguinale, with Rectal Manifestations in Child, Am. J. Dis. Child. **49**:703-709 (March) 1935. (*b*) Dick, W.: Ist das Lymphogranuloma inguinale auf die Nachkommenschraft übertragbar? Med. Klin. **32**:319-320 (March 6) 1936. (*c*) Banciu, A., and Caratzali, A.: Un cas de maladie de Nicolas et Favre à manifestations multiples, Ann. dermat. et syph. **9**:100-105 (Feb.) 1938. (*d*) Sonck, C. E.: Five Cases of Lymphogranuloma Inguinale in Children (with Rectal Manifestations and Arthropathies), ibid. **20**:171-190 (March) 1939. (*e*) Gulowsen, G.: Nord. med. **4**:3518, 1939, cited by Winge, M.: Über lymphogranuloma inguinale unter besonderer Berücksichtigung des Vorkommens bei Kindern, Klin. Wchnschr. **43**:1073-1076 (Oct. 25) 1941. (*f*) Sonck, C. E.: Sixth Case from Finland of Lymphogranuloma Inguinale in Children, Acta dermat.-venereol. **21**:469-472 (May) 1940. (g) Winge, M.: Über lymphogranuloma inguinale unter besonderer Berücksichtigung des Vorkommens bei Kindern, Klin. Wchnschr. **43**:1073-1076 (Oct. 25) 1941.

panying table. A study of the table reveals some interesting data. Eleven patients are girls; two are boys. Eight patients had only rectal manifestations of lymphogranuloma venereum, five had both inguinal adenitis and rectal lesions. Of the 13 cases, 11 have been reported from European countries.

The following is a case report of the youngest boy with a rectal stricture due to lymphogranuloma venereum. The diagnosis was confirmed by a positive complement-fixation reaction and a positive Frei reaction.

REPORT OF CASE

J. G., a 10-year-old Negro boy, entered the medical college clinic on Jan. 9, 1951, with the chief complaint of "pain in stomach" of two months' duration. For the preceding six months he had straining with bowel movements, rectal bleeding, and narrow or thin stools—these symptoms had been gradual and progressive. There were usually three or four movements a day. The stools were usually in "small pieces." He occasionally took magnesia magma. During repeated interviews he denied any unusual sexual behavior.

Past History.—He was born Jan. 2, 1941. Gestation had been to full term. His development had been normal. Of interest was an episode of conjunctival injection and ulcer of the cornea in September, 1949. He was treated at the eye clinic, at which time a diagnosis of phlyctenular keratoconjunctivitis was made.

Family History.—The mother denied any symptoms suggestive of lymphogranuloma venereum. The three sisters, ages 7 years, 4 years, and 2 months, were normal. The complement-fixation reactions for lymphogranuloma venereum for the mother and the three sisters were negative. The father would not come in for examination.

Physical Examination.—On admission no abnormality was noted except for the presence of palpable and discrete lymph nodes of the anterior cervical, posterior cervical, axillary, epitrochlear, and inguinal regions, and the rectal stricture. There were no hemorrhoids, fissures, fistulae, or scars in the perianal area. Spincter tone was normal. At 8 cm. from the anus there was a single annular stricture of hard, regular consistency. This stricture was classified as Type 3, i. e., having a small amount of scar tissue in the submucosa and muscularis, and put in Grade 4, i. e., being 0.6 cm. in diameter. This classification and grading of the strictures follows the system used in this clinic and described in a previous report.[2]

Laboratory Examinations.—The urine was normal. Examination of the blood disclosed a hemoglobin level of 11 gm., a red cell count of 4,950,000, a white cell count of 8,400, with 57% lymphocytes, 11% monocytes, 30% neutrophiles, and 2% eosinophiles. Blood tests (Kline and Kolmer) for syphilis gave negative reactions. The complement-fixation reaction for lymphogranuloma venereum was positive to 1 : 512 dilution. The total serum protein was 8.25 gm., the albumin 4.95 gm., the globulin 3.30 gm. The feces showed no ova or protozoa. Biopsy of the rectal lesion showed "proctitis, acute and chronic." The Frei reaction was positive. The roentgenogram of the chest was normal.

Course.—The patient was treated with chloramphenicol (chloromycetin®) capsules, 250 mg. three times a day for 35 days, but with no dilatations of the stricture. During this time the patient reported no rectal bleeding and no straining at the stool. Two months later, because the rectal stricture seemed to be narrowing, the patient was given chloramphenicol again, 250 mg. four times a day for seven days, then 250 mg. three times a day for nine more days. The complement-fixation reaction was not affected by the chloramphenicol. During and after chloramphenicol treatment the complement-fixation tests were repeated, and the reactions remained positive in the dilutions of 1 : 256, 1 : 256, and 1 : 512. Digital dilatations of the stricture were carried out at weekly intervals for two months. At the end of this time the stricture was classified as Grade 3, i. e., being 1.2 cm. in diameter, whereas on admission the stricture was classified as Grade 4, i. e., being 0.6 cm. in diameter.

2. Banov, L., Jr.: Aureomycin Treatment of Rectal Strictures, Am. Surgeon **16**:143-149 (Feb.) 1951.

COMMENT

The question arises how this patient contracted lymphogranuloma venereum. In many interviews he denied any sexual contacts. The mother had never given enemas prior to the present illness. It is possible that the episode of conjunctivitis which occurred about a year prior to the symptoms of proctitis and rectal stricture was another manifestation of lymphogranuloma venereum. At that time, however, no Frei test or complement-fixation test was carried out.

SUMMARY

Case reports of rectal lesions of lymphogranuloma venereum in childhood have been tabulated from the world literature.

From the paucity of case reports, it seems that rectal manifestations of lymphogranuloma venereum in children are rare.

A case of a 10-year-old boy with a rectal stricture due to lymphogranuloma venereum has been presented. The diagnosis was confirmed by positive complement-fixation and Frei reactions.

This patient is the youngest boy with a rectal stricture due to lymphogranuloma venereum reported thus far in the literature.

The chloramphenicol used was supplied through the courtesy of Parke, Davis & Company, Detroit.

PRIMARY MALIGNANT TUMOR OF THE PANCREAS IN A FIFTEEN-MONTH-OLD BOY

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AND
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PRIMARY malignant tumor of the pancreas is extremely rare in infancy and childhood. An extensive review of the literature disclosed only two primary sarcomas [1] and six primary carcinomas [2] with histological diagnostic confirmation. In all reported cases the disease has been fatal.

The lymphosarcomas were located only in the pancreas and occurred in a 4-year-old boy and a 9-day-old girl. In the latter the disease was discovered at autopsy, after death had resulted from peritonitis and liver abscess secondary to an omphalitis and phlebitis of the umbilical vein.

Of the six adenocarcinomas, three were described as cylindrical-cell, one was medullary, and two were not further classified. Three originated in the head of the pancreas, one in the head and body, one in the tail, and one was not localized. The tumor mass was palpated in two instances, jaundice was evident in two cases, diarrhea was striking in two cases, constipation in one, edema of the lower extremities in one, and a markedly distended abdomen in one. Metastases were found in the adjacent retroperitoneal and periportal lymph nodes in three instances, in the liver in five instances, in the lungs in two, and in the kidneys and duodenum in one. The ages of the patients ranged from 6 months to 13 years. There were three boys and two girls. (In one the sex was not recorded.) All patients presented anorexia and pallor of varying degrees.

Because of the rarity of this condition, the following case of a primary embryonal cancer of the head and body of the pancreas was deemed worthy of recording. The outstanding presenting features were an abdominal mass and a celiac-like syndrome.

REPORT OF A CASE

C. W., a 15-month-old white boy, was hospitalized for evaluation of a small, centrally located, deep upper abdominal mass. He had apparently been in excellent health until three weeks prior

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From Children's Hospital.

1. Litten: Sarcome primitif du pancreas, Semaine méd., Paris, 1888. L'Huillier, A.: Über einen Fall von kongenitalem Lymphosarkom des Pankreas, Arch. path. Anat. **178**:507, 1904.

2. Bohn, A.: Krebs der Leber, der portalen und retroperitonealen Lymphdrüsen und des Pankreas bei einem halbjährigen Kinde, Jahrb. Kinderh. **23**:144, 1885. Kühn, A.: Über primäres Pankreascarcinom im Kindesalter, Klin. Wchnschr. **24**:494, 1887. Simon, F.: Über ein Pankreascarcinom bei einem 13 jährigen Knaben, Griefswald, J. Abel, 1889. Stewart, S. C., and Stewart, L. F.: A Case of Cancer of the Pancreas in a 9 Year Old Boy, Internat. Clin. **2**:118, 1915. Stout, B. F., and Todd, D. A.: Report of a Case of Primary Adenocarcinoma of the Pancreas in a 4-Year-Old Child, Texas J. Med **28**:464, 1932. Corner, B. D.: Primary Carcinoma of the Pancreas in an Infant Aged 7 Months, Arch. Dis. Childhood **18**:106, 1943.

to admission, when he began passing daily four to eight large, mushy, light-yellow, foul-smelling, foamy, greasy stools with undigested food particles. Anorexia, pallor, irritability, and a weight loss of 5 lb. (2,300 gm.) were prominent features.

A maternal uncle had had a pancreatic cyst removed some years previously. Otherwise the family history was noncontributory.

Physical examination on admission disclosed a pale, moderately malnourished boy who seemed chronically ill. The blood pressure was 105 degrees of mercury systolic and 60 degrees of mercury diastolic, the pulse rate was 120, respirations were 20 per minute, and the temperature was 99.2 F. Deep palpation of the epigastrium revealed a walnut-sized, hard, nodular, immovable mass situated in the midline in the region of the pancreas and kidney pelves. The remainder of the examination disclosed no other abnormality.

Urinalyses done on the following two days disclosed 200 to 500 mg. of albumin per 100 ml., 2 to 10 white blood cells, and 3 to 5 erythrocytes per high power field. An intravenous pyelogram and a chest roentgenogram were within normal limits. A blood count revealed 10 gm. of

Summary of Primary Malignant Tumors of the Pancreas in Infants and Children

Author and Date	Age	Sex	Pancreatic Tumor	Signs and Symptoms	Metastases
Litten, 1888	4 yr.	M	Lymphosarcoma	.....	.....
L'Huillier, 1904	9 days	F	Lymphosarcoma	Omphalitis, phlebitis of umbilical vein, liver abscess, peritonitis	None
Bohn, 1885	6 mo.	..	Adenocarcinoma of head	Abdominal tumor, jaundice	Liver, portal and retroperitoneal lymph nodes
Kühn, 1887	2 yr.	F	Cylindrical-cell adenocarcinoma	Diarrhea, edema of legs	Liver, lungs, adjacent lymph nodes
Simon, 1889	13 yr.	M	Adenocarcinoma of head and body	Diarrhea, jaundice	Liver, kidney, duodenum
Stewart and Stewart, 1915	9 yr.	M	Medullary carcinoma of tail	Constipation	.....
Stout and Todd, 1932	4 yr.	M	Cylindrical-cell adenocarcinoma of head	Abdominal mass for 2 weeks	Adjacent lymph nodes, liver
Corner, 1943	7 mo.	F	Cylindrical-cell adenocarcinoma of head	Distended abdomen, dilated veins	Liver, pleural surface of lungs, anterior mediastinal lymph glands
Warthen, Sanford, and Rice, 1952	15 mo.	M	Embryonal adenocarcinoma of head and body	Abdominal mass, celiac syndrome, jaundice	Hepatic triad, superior mesenteric lymph nodes, splenic capsule, lung

hemoglobin, 3,100,000 red blood cells, and 7,000 white blood cells, with a normal differential distribution. Trypsin was absent from the stools on three occasions in 1:5 and 1:10 dilutions. A stool culture was negative for pathogens.

Five days after admission the abdominal mass had enlarged to the size of a lemon, and a typical diarrhea diet had failed to alter the character of the stools. In view of the celiac-like stools, absence of trypsin from the stools, and a normal intravenous pyelogram study, compression of the pancreatic duct by the enlarging abdominal mass was postulated. A preoperative diagnosis of a large solitary pancreatic cyst or pancreatic tumor with hemorrhage into the pancreas was entertained, and on the sixth hospital day an exploratory laparotomy was performed (M. C. S.).

With the patient under general anesthesia, the abdominal cavity was exposed, and when the lesser peritoneal sac was entered a tumor was noted involving the entire anterior portion of the head and body of the pancreas. This mass was closely adherent to the common bile duct, portal vein, and hepatic artery. Its capsule was intact, and aspiration of its soft cystic center yielded a yellow bloody fluid. A portion of the tumor removed for biopsy and examined by a frozen-section technique disclosed "a round-cell tumor, its exact nature undetermined." There was no evidence of distant metastases. The pancreatic capsule was incised and the tumor resected, care being exercised to preserve the normal-appearing tissue in the tail and in the posterior body and head. It was not possible to remove all the growth under the common duct, portal vein, and hepatic artery.

Postoperative x-ray therapy to the region of the pancreas was administered for nine days with a total of 1,458 r. The stools appeared relatively normal for several weeks, later reverting to a celiac-like character. Trypsin was absent from the stools on nine occasions postoperatively, and the cystic fluid obtained from the pancreatic tumor at the time of surgery showed no tryptic activity. Fasting blood sugars ranged from 60 to 90 mg. per 100 ml., and the blood count was within normal limits. No abnormalities were noted in roentgenograms of the skull and long bones.

After three weeks of an uneventful postoperative course the patient was transferred to a convalescent home with a diarrhea-controlling diet and supplemental multiple vitamins and pancreatin granules. The celiac-like stools became more prominent, and weight loss continued. Four weeks later an icteric tint appeared on the skin and the sclerae, and the patient was returned to the hospital for further study. Physical examination disclosed mild icterus of the skin, the sclerae, and the mucous membranes, a well-healed upper abdominal incision, and an indefinite mass in the epigastrium and in the right upper quadrant. Laboratory studies were directed toward determining whether the source of the jaundice was extrahepatic or intrahepatic. Urine urobilinogen was absent upon three determinations, and bile was present on several occasions. The prothrombin time was normal, the serum thymol turbidity reading was 8.1 units, total serum protein was 9.3 gm. with a serum albumin of 3.82 gm., a serum globulin of 5.56 gm., and an albumin globulin ratio of 0.7 to 1. A 24-hour quantitative stool analysis revealed 2 mg. of urobilinogen per 100 gm. of feces. Shortly after admission the total serum bilirubin level was 4.32 mg. per 100 cc. (prompt direct, 2.94 mg., indirect, 1.38 mg.). Eight days later the total serum bilirubin had risen to 16.0 mg. per 100 cc. (prompt direct, 10.6 mg., indirect, 5.4 mg.). Cephalin-cholesterol flocculation was 3+ in 48 hours; in three examinations trypsin was absent from the stools in 1:5 and 1:10 dilutions; roentgenograms of the chest and abdomen were not abnormal, and several blood counts disclosed merely a microcytic hypochromic anemia.

In view of the laboratory findings and the rapidly progressing jaundice, liver metastases were considered unlikely, and a diagnosis of common-bile-duct obstruction was made. Although envelopment of the periportal ductal system by metastasizing tumor tissue was considered most likely, an exploratory laparotomy was performed because of the remote possibility of post-irradiation scar-tissue stricture of the common bile duct.

With the patient under general anesthesia, the abdomen was reentered, and after aspiration of a large amount of ascitic fluid it was noted that the tumor had recurred and was as large as that encountered at the first operation. In addition, it had completely surrounded and infiltrated the portal triad. The gall bladder had tripled its size and was tightly distended with white bile. A palliative cholecystojejunostomy was performed and the abdomen closed.

The postoperative condition was extremely poor, and although the jaundice cleared almost completely the patient was never able to retain food by mouth and was consequently maintained parenterally. A slow progressive decline ensued, with superimposed chickenpox. Twenty days after operation, convulsive movements of the left side of the face, the left arm, and the left leg developed. The left pupil was more dilated than the right. The patient became unresponsive and shortly thereafter died.

Necropsy.—Significant gross findings were limited to the pancreas, the hepatic and common bile ducts, the hepatic artery, the portal vein, the right lung, and the mesenteric lymph nodes. A large, firm, light-yellow tumor mass, 5 cm. in diameter, arose from the head and body of the pancreas and extended along the common bile duct and hepatic ducts to reach the liver. Tumor tissue had also invaded the lymph nodes surrounding the superior mesenteric root. The common bile duct, the hepatic artery, and the portal vein were completely encircled by the invading tissue, and sectioning disclosed the lumen of the common bile duct to be completely occluded from the ampulla of Vater to the opening of the cystic duct. Proximal to this point and on into the liver substance the hepatic ducts were markedly dilated. No invasion of the liver parenchyma was detected; however, biliary cirrhosis with numerous "bile abscesses" was prominent. A firm tumor nodule, 1 cm. in diameter, was present on the posterior surface of the upper lobe of the right lung. Permission for examination of the brain was not granted.

Microscopic examination of the pancreatic tumor tissue revealed an irregular syncytial mass of small round and spindle cells with faintly eosinophilic and sparse cytoplasm with hyperchromatic nuclei containing numerous mitotic figures. The intercellular matrix was composed of

fibrous connective tissue, and interspersed throughout the tumor were pancreatic ducts lined with cuboidal cells, poorly defined islands of Langerhans, and small groups of incompletely formed acini. Similar tumor cells were present adjacent to and infiltrating a section of the splenic capsule, in the well-circumscribed lung mass, in the hepatic triad including the lumen of the common bile duct, and in the mesenteric lymph nodes.

Histopathological Diagnosis.—The following histopathological diagnosis was made: (1) embryonal adenocarcinoma of the head and body of the pancreas, with metastases to the hepatic triad, the lumen of the common bile duct, the superior mesenteric root, the splenic capsule, and the right lung; (2) marked biliary cirrhosis with "bile abscesses" of the liver, and (3) biliary nephrosis.

Tissue from the pancreatic tumor was submitted to the Tumor Registry of the American Academy of Pediatrics with the following suggested diagnoses: (1) small round-cell tumor of pancreas, probably malignant (Roger D. Baker); (2) sarcoma, possibly rhabdomyomatous (A. G. Foord); (3) anaplastic or embryonal adenocarcinoma of pancreas (E. Clarence Rice); (4) malignant embryonal tumor (Paul E. Steiner); (5) embryonal rhabdomyosarcoma (Fred W. Stewart).

SUMMARY

A case of primary embryonal cancer of the head and body of the pancreas in a 15-month-old boy is reported.

The eight previously reported primary malignant tumors of the pancreas in infants and children are reviewed briefly.

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Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

HYDROLYSED CASEIN FOR PARENTERAL ADMINISTRATION TO INFANTS. YVONNE J. WILLIAMS, E. A. BISHOP, and W. F. YOUNG, Arch. Dis. Childhood **24**:159 (Sept.) 1949.

Intravenous infusions of an enzymic digest of casein ("casydrol") with dextrose have been given to 61 infants without any reactions being observed. Necropsy findings suggest that there was an embolic spread of infection in one case as the result of the infusion, while in three others this complication might have been due to the infusion but was more probably due to a focus of infection already present in the body. An infusion of 2.5% "casydrol" in 5% dextrose solution was well tolerated by the veins. A "closed" method of administering fluids intravenously must be used to safeguard patients from the risks of contamination of the infusion.

Twenty-six infants received infusions of "casydrol" for a period of several days, so that the treatment was likely to have affected the course of their disease, and of these, 19 survived and 7 died. Other factors, such as plasma and blood transfusions and parenteral supplements of vitamin preparations, probably contributed to the good results in the patients who recovered.

Further knowledge of the nitrogen metabolism of sick and convalescent infants is needed, so that a full use may be made of the preparations now available for intravenous administration.

KELLY, Milwaukee.

SOME PECULIARITIES OF BODY COMPOSITION AND WATER DISTRIBUTION IN INFANTS' ATROPHY. E. KERPEL-FRONIUS and K. FRANK, Ann. pædiat. **173**:321 (Nov.) 1949.

The atrophy of the body does not affect all organs or systems of organs equally: Some organs, such as the brain, the kidney, the skeleton and even the skin, go on growing or atrophy to a lesser extent than the total body. Thus their relative share in the body of an atrophic child is far greater than in a normal person. Other organs, e. g., the fatty tissues and the muscles, atrophy much more than the total body. Through the loss of fat the organism of the atrophic child will thus contain—if the total water remains the same—relatively more water. A change of water distribution is brought about with the increase of extracellular water and the decrease of intracellular water. The reason for this change is difference in the rate of atrophy in the various systems of organs. The organs which are richer in extracellular water participate less in the process of atrophy than the muscles, which contain a greater part of cell water. The water distribution is very much like that of premature babies. The atrophy of the heart is greater than that of some other organs which require a particularly large share of the intrinsic blood supply. This fact seems to be unfavorable for the circulation of atrophic children.

FROM THE AUTHORS' SUMMARY.

ACIDOSIS AND ALKALOSIS IN THE CLINIC. J. ALVAREZ DE LOS COBOS, Bol. méd. hosp. inf. México **7**:185 (April) 1950.

The clinical aspects of the different types of acidosis and alkalosis are discussed from the diagnostic, pathogenic, and therapeutic points of view. Hartmann's classification has been followed. After a reminder of the normal figures for CO_2 and pH, attention is called to the seriousness of the syndromes of acidosis and alkalosis when there is a deviation from such figures.

According to most authors, acidosis has a much greater incidence than alkalosis, and is most frequently seen in infants' diarrhea with dehydration. Next in order of frequency is the acidosis seen in diabetes, which in the author's hospital is considered of low incidence. Also,

there is renal acidosis, especially of the chronic type, caused by chronic nephritis. Mention is also made of the acidosis due to serious infections, which is usually accompanied by ketosis.

The most important type of alkalosis, that which is the result of a high pyloric or intestinal obstruction or of fistulas in the first portion of the small intestine, has not been seen in this hospital; this is possibly due to the early medicosurgical attention given to congenital hypertrophic pyloric stenosis. It is interesting to remember the presence of tetany in this lack of acid-base balance. It is thought that this syndrome may possibly have been seen in some cases of acidosis with abundant vomiting and little diarrhea which had been overtreated. Other types of alkalosis are those due to obstructive vomiting and excessive administration of bases, and the respiratory type. All these are very infrequent.

A brief review is given of the forms of treatment advised by Hartmann with the modifications introduced at the Hospital Infantil of Mexico. FROM THE AUTHOR'S SUMMARY.

Vitamins; Avitaminoses

ABSORPTION OF ALPHA TOCOPHEROL AND TOCOPHERYL ESTERS BY PREMATURE AND FULL-TERM INFANTS AND CHILDREN IN HEALTH AND DISEASE. LLOYD J. FILER, JR., STANLEY W. WRIGHT, MARY PARKE MANNING, and KARL E. MASON, Pediatrics **8**:328 (Sept.) 1951.

The ability of premature and full-term infants in health and disease to absorb vitamin E (tocopherol) was determined by using the technic of multiple withdrawals of small samples of capillary blood at three-hour intervals following an oral dose of α-tocopherol or α-tocopherol esters.

Premature infants were found to absorb vitamin E as well as full-term infants, when compared on the basis of the area under the curve for a 12-hour period following an oral dose of tocopherols at 20 mg. per kg. body weight. This is in marked contrast to the diminished ability of the premature infant to utilize vitamin A and fats.

In a series of 29 infants, those with disease states diagnosed as fibrocystic disease of the pancreas, diarrhea, and cirrhosis, were characterized by a poor response to the test, i. e., the tolerance curve was low. Other infants, those with a variety of disorders not associated with fat or fat-soluble vitamin intolerance, had characteristic absorption curves with a maximum nine hours after receiving oral tocopherol.

In a series of 14 children and 1 adult, patients with sprue, celiac syndrome, and lupus erythematosis were noted to absorb tocopherols poorly. Metabolic disorders with associated hypercholesterolemia were observed to give abnormally high values for the area under the curve.

A comparison of vitamin A absorption with vitamin E or tocopherol absorption in a series of 10 observations indicated that patients responding poorly to one test did poorly in both.

No difference in response was noted when various esterified forms of tocopherol were administered in place of α-tocopherol. This is contrary to the reported increase in biologic potency (rat assay) of the esterified forms of tocopherol.

An index calculated from the fasting and nine-hour levels of serum tocopherol, which was corrected for the tocopherol equivalents supplied by the ester forms, compared favorably with the area measurements and failed to demonstrate any difference in absorption of the free versus ester tocopherol. FROM THE AUTHORS' SUMMARY.

Prematurity and Congenital Deformities

677 CONGENITALLY MALFORMED INFANTS AND ASSOCIATED GESTATIONAL CHARACTERISTICS: II. PARENTAL FACTORS. JANE WORCESTER, STUART STEVENSON, and ROBERT RICE, Pediatrics **6**:208 (Aug.) 1950.

The obstetric records of all mothers who gave birth to congenitally malformed infants, live or stillborn, in the Boston Lying-In Hospital during the years 1930 through 1941, together with the pediatric records of their live babies during the neonatal period, have been abstracted and analyzed. Statistical evaluation of data from such a source offers a means to study the origin of

congenital anomalies; and many factors have been found to be associated with pregnancies which result in the birth of defective infants. The statistical method presents several difficulties, however, and it must be used with careful regard for proper sampling and controls if fallacious conclusions are to be avoided. It is suggested that in future studies from large maternity hospitals analysis of all neonatal deaths and stillbirths be made in conjunction with analysis of defective infants. Such analysis of current records both of malformed and of normal infants should serve eventually to clarify the relations between the factors and to indicate which are the causes and which the effects.

During a 12-year period, 29,024 infants were born in the Boston Lying-In Hospital, and 677 of these were described as defective; 483 of these had valid diagnoses, giving a rate of 1.7%. Malformed infants accounted for 15.9% of the total stillbirths and 13.2% of the total neonatal deaths. In 32% of the malformed infants who died in the neonatal period there were defects referable to the cardiovascular system and in 27% to multiple deformities. In 79% of the malformed stillbirths, the fetus had defects of the central nervous system.

Twinning occurred with approximately twice the expected frequency. Since twinning in itself may represent an anomaly or may be found with anomalies, it might prove instructive to explore environmental circumstances associated with an unusual frequency of twinning in a larger series.

Defects which appeared in the early months of gestation, or which presumably required more than one month for their formation, caused the highest neonatal mortality. Approximately one-third of the infants had defects which required more than one month for their formation.

The total anomaly rate was significantly high in 1935, when births of defective infants reached a peak seven months after a widespread epidemic of rubella. These data were recorded before the teratogenic properties of this disease were suspected and are not subject to the bias which may complicate information currently being gathered. They suggest the relationship between rubella and congenital anomalies. This material offers, furthermore, a method of attack on the problem of congenital anomalies which can be used more effectively than it has been in the past.

The number of births of infants whose anomalies presumably required more than one month for their development was consistently high in the third and fourth quarters of the year. This dates their conceptions and organogenetic periods in the fourth and first quarters of the year, a time that respiratory diseases are common. Speculation as to possible association is not prudent, but these results are of sufficient interest to suggest that an attempt should be made to confirm them.

With the exception of mothers of mongoloid infants, who are older, the age distribution of the mothers of surviving defective infants corresponds closely with that of mothers of all live-born infants in Massachusetts during 1930 to 1941 and with that of a sample of 1,000 mothers delivered in the Boston Lying-In Hospital. Because of the nature of the control groups, however, it is not possible to conclude that mothers of surviving malformed infants do not differ in age from mothers of live-born infants in general.

Mothers of the malformed infants who died before 10 days of age were significantly older than mothers of surviving defective infants, and the neonatal mortality of normal infants shows the same association with advanced maternal age. Thus, the age of the mother appears to be of importance in the survival of the infant but may have little significance in the causation of congenital malformations. It is possible that several observers have suggested age as a teratogenic factor because, in an attempt to obtain series of defective infants with confirmed diagnoses, their material has thus become heavily weighted by the number of dead babies.

Only 11 mothers in this series gave birth to two malformed infants in the Boston Lying-In Hospital. The rate of previous birth of malformed infants to mothers in this series was 4.8%. The rate for the entire hospital population was 1.7%.

Polyhydramnios occured in 10% of the pregnancies; 60% of these resulted in the birth of anencephalic infants. The frequency of polyhydramnios is thus negligible in this series except when the pregnancy results in anencephaly.

Only 1% of the mothers gave a history of febrile illness in the first trimester of pregnancy. It seems probable that the average pregnant woman is unable to recall minor illnesses which afflicted her at a time when she may not even have known that she was pregnant. From such a viewpoint, the limitations of questionnaires are apparent.

A history of febrile illness at some time during the last two trimesters of pregnancy was given by 12.4% of the mothers. However, six of the mothers of the 11 surviving infants with congenital hydrocephalus as a single defect had illneses late in pregnancy. It is suggested that maternal infections other than syphilis and toxoplasmosis may be important in the causation of hydrocephalus when this occurs as an isolated defect.

Twenty-one per cent of the mothers who gave birth to infants with multiple anomalies suffered from chronic illness, as compared with 9.9% of the mothers in the total series.

The frequency of severe maternal heart disease was not unusual (the sampling seems valid), and maternal heart disease does not appear to be an important factor in the causation of congenital anomalies.

The authors state that 11.5% of the mothers who gave birth to infants with congenital heart disease and 14.6% of the mothers bearing infants with multiple anomalies vomited with sufficient frequency to merit note of it in their records. This contrasts with a rate of 5.2% for mothers in the total series.

Thirteen and five-tenths per cent of the mothers were classified as toxemic, a rate which does not differ significantly from the rate for mothers of normal infants. It contrasts, however, with the rates of 17% for mothers bearing infants with congenital heart disease and 19% for mothers who gave birth to infants with multiple anomalies.

Thirteen per cent of the mothers gave a history of threatened abortion. This rate seems high, and among mothers of infants with multiple malformations it reached 25%. Further investigation is necessary to determine whether antepartum bleeding is a cause or an effect of malformation.

Chronic illness, vomiting, toxemia, and threatened abortion are found with increasing frequency as complications of pregnancy in those women bearing defective infants who died in the neonatal period. Thus, these conditions may be found often when a sample of dead malformed infants and their mothers is studied. This may lead to fallacious conclusions.

Placentas in this series were not more frequently abnormal than in a control group of pregnancies, and it seems unlikely that faulty placentation as such is a frequent cause of congenital anomalies.

Thirty-nine and four-tenths per cent of the mothers had hemoglobin levels below 75%. This frequency of anemia is greater than can be considered physiological and is of interest in view of the possible role of anoxia as a teratogenic agent. Hemoglobin determinations should be performed routinely in antepartum clinics, and the role of maternal anemia in the etiology of congenital anomalies should be studied more thoroughly.

Twenty-six and five-tenths per cent of the infants weighed less than 2.4 kg., and 25.5% of them were born more than 17 days previous to their mothers' expected dates of confinement. These rates are significantly high, and it may be concluded that prematurity occurs oftener in malformed infants. All premature infants should be carefully examined, therefore, for evidences of congenital defects. They should be divided into malformed and normal groups when studies of mortality and morbidity are made concerning them. FROM THE AUTHORS' SUMMARY.

Acute Contagious Diseases

ANTIBIOTIC TREATMENT OF PERTUSSIS. LLOYD N. HAZEN, GEORGE GEE JACKSON, CHANG, SHIH-MAN, EDWIN H. PLACE, and MAXWELL FINLAND, J. Pediat. **39**:1 (July) 1951.

When chloramphenicol, aureomycin, or terramycin were given to patients with whooping cough in doses of 60 mg. per kilogram per day, Hemophilus pertussis disappeared from pharyngeal cultures after three or four days. Treatment was continued for 10 days. These drugs were

also equally effective in improving the general condition of the patients and in decreasing the severity and number of paroxysms. This improvement in clinical appearance was most striking in children under one year old.

Despite the fact that H. pertussis did not reappear in nasopharyngeal cultures, some patients had exacerbation of cough when the use of the antibiotic was stopped. Penicillin had little if any effect upon whooping cough. It is possible that aureomycin, chloramphenicol, or terramycin may, by suppressing H. pertussis, delay and reduce antibody response.

MACDONALD, Pittsburgh.

THE PATHOGENESIS OF THE ACUTE EXANTHEMS: AN INTERPRETATION BASED ON EXPERIMENTAL INVESTIGATIONS WITH MOUSEPOX (INFECTIOUS ECTROMELIA OF MICE). FRANK FENNER, Lancet **2**:915 (Dec. 11) 1948.

The onset of symptoms in smallpox, chickenpox, and measles is not the period of "invasion," according to Fenner. On the basis of experiments with mousepox virus, he suggests that in these diseases the blood stream and organs are invaded during the incubation period before symptoms arise. In mousepox the virus passes from the portal of entry, the skin, to the regional lymph node, where it multiplies. Lymph-node necrosis then liberates virus into the blood stream, where it is immediately taken up by phagocytes of the liver and spleen and possibly the bone marrow. The virus is concentrated greatly in these organs and is finally released directly into the blood stream by necrosis of infected cells lining the sinusoids. The secondary viremia thus produced is followed by widespread focal infection of the epidermal cells. The virus then multiplies in the skin for several days before macroscopic lesions appear.

Allergic reaction to mousepox virus could not be demonstrated until after the virus had become localized in the skin. The skin lesions, Fenner says, are therefore not primarily allergic in nature, and, he hypothesizes, the same might be said for the skin lesions of variola and vaccinia, alastrim, measles, and chickenpox.

MACDONALD, Pittsburgh.

THE VALUE OF MESTER'S REACTION AND ITS MODIFICATIONS IN THE DIAGNOSIS OF RHEUMATIC INFECTIONS OF CHILDREN. E. ORLANDI, Lattante **21**:471 (July) 1950.

Mester's reaction, as used by Orlandi, calls for the intradermal injection in the forearm (2 wheals) of 1 cc. of 0.1% salicylic acid. The child is in the fasting state. White blood counts are made before and 30 minutes and 60 minutes after the injection. If the white count has fallen up to 15% between the initial and the 30-minute count, the test is regarded as doubtfully positive; if it has fallen between 15 and 20%, the test is positive, and if over 20%, strongly positive. The white count will usually return to the fasting figure on the 60-minute count.

Control injections of distilled water and of isotonic sodium chloride solution did not affect the white blood count.

Mester's test was positive in 28 of 34 children with rheumatic infections. It was positive in only 3 of 18 children with other infections. These three children had hepatitis. The question is raised of a possible similarity of the etiological agents of hepatitis and rheumatic infection.

HIGGINS, Boston.

THE PROBLEMS OF SALMONELLA INFECTIONS IN INFANTS. P. FORNARA, Lattante **22**:385 (July) 1951.

The rate of infant mortality in Italy is about 2 to 3 times the rate in the countries of western Europe and in the United States. Enteritis is largely responsible for this higher rate.

Salmonella organisms are found in the stools of about 5% of infants with diarrheal infections. Epidemics rather than sporadic cases are the rule. Usually the disease can be traced to a human carrier. Although the Salmonella typhimurium is the most commonly found type of Salmonella, rodents do not appear to be the direct source of the infections. Meningitis is

sometimes a complication of the disease in the very young infants. The fatality rate for infants with paratyphoid infections (6%) is less than the rate in patients over 50 years of age (15%). The sulfonamides are not so efficacious in paratyphoid fever as in bacillary dysentery.

HIGGINS, Boston.

SALMONELLA INFECTION IN A 29-DAY-OLD INFANT. A. SIMONINI, Lattante **22**:418 (July) 1951.

A 29-day-old baby became mildly sick with paratyphoid fever, proved by serological studies. Paratyphoid fever had developed in the mother of the child 10 days earlier; the baby was bottle fed.

HIGGINS, Boston.

PHENOSULFAZOLE IN THE TREATMENT OF HUMAN POLIOMYELITIS. T. PORCELLI, Pediatria **58**:744 (Sept.) 1950.

Phenosulfazole ("darvisul") proved of no benefit, when tried in the treatment of 23 cases of acute poliomyelitis at the Children's Hospital in Milan.

HIGGINS, Boston.

FILTRABLE VIRUSES AND THE EXANTHEMAS. G. CARONIA, Pediatria **59**:469 (July) 1951.

Photomicrographs, using the electron microscope, illustrate cultures of viruses from patients with scarlet fever, chickenpox, measles, and roseola.

HIGGINS, Boston.

REMARKS CONCERNING POLIOMYELITIS THEORY AND THERAPY OF SISTER KENNY. GERT SEESER, Deutsche med. Wchnschr. **76**:709 (May 25) 1951.

The theory of Sister Kenny, that poliomyelitis is a disease of the muscles and connective tissue with primary localization of the causative agent in those tissues, cannot be accepted. With regard to therapy, the author emphatically insists that all sensory stimulations should be omitted in the acute stage and that exercise therapy should be instituted only after immobilization for six to eight weeks. At this time, in argument with the therapy of Sister Kenny, the treatment of the muscles with a tendency to contractures becomes necessary.

AMBERG, Rochester, Minn.

NEW METHOD FOR TREATMENT OF TOXIC DIPHTHERIA: PRELIMINARY REPORT. HELMUT GRUTZMANN, Med. Klin. **46**:517 (April 27) 1951.

Diphtheria antitoxin was administered by continuous intravenous drip, using a Behring preparation (Fermo-Serum) in which the foreign proteins are disintegrated to a great extent. Five female patients, including one 7 years old, recovered from an infection which would probably have been fatal. Two other children, both 3½ years old, and one adult died; all had an additional complication. Postdiphtheritic injuries could not be prevented.

AMBERG, Rochester, Minn.

VALUE OF PYRAMIDON THERAPY IN POLIOMYELITIS. A. WINDORFER and E. GEISSER, Med. Klin. **46**:1076 (Oct. 12) 1951.

Sixty-two children with poliomyelitis received aminopyrine (pyramidon®) according to the recommendation of Deuretsbacher; seventy-one patients with poliomyelitis did not receive the drug. When administered to patients in the febrile state the temperature dropped to normal somewhat more rapidly in those treated. No effect was noted in the incidence or on the progress of paralysis. Large doses of aminopyrine often produced vomiting and loss of appetite. Aminopyrine in the usual dosage may be of advantage to combat pain.

AMBERG, Rochester, Minn.

USE OF THE ELECTROMICROSCOPES FOR THE DIAGNOSIS OF VACCINIAL DISEASES. F. PUNTIGAM and E. ORTH, Wien. klin. Wchnschr. **63**:817 (Oct. 26) 1951.

A boy 7 years of age, never vaccinated, was hospitalized with numerous small vesicles widely distributed. A "varioliform" disease was suspected. No typical micro-organism could be found electromicroscopically, and the Paul test elicited a negative reaction. To the contrary, a young boy vaccinated previously, without success, was admitted with the diagnosis of skin diphtheria in the region of an ear lobe. In the content of the pustule typical elements of variola vaccine were demonstrated. The reaction to the Paul test was positive, and Guarnieri bodies were seen in the cornea. Another unsuccessfully vaccinated boy had several encrusted lesions on the face. In such a crust typical vaccine bodies were demonstrable by the electron microscope. The result of the Paul test was positive, and Guarnieri bodies were demonstrable in the cornea. In both of these cases, no history of contact with freshly vaccinated children could be obtained. A boy about 13 years of age was vaccinated against smallpox; a week later cerebral symptoms developed. A diagnosis of vaccinal encephalitis was made; in the slightly turbid cerebrospinal fluid, with increased cell count, vaccinia elements were demonstrable, and the Paul test reaction was positive. It is stated that the virus of chickenpox and variola vaccine can easily be distinguished electromicroscopically.

AMBERG, Rochester, Minn.

COMBINED VACCINATIONS. FERENC FARAGÓ, Paediat. danub. **4**:220 (Oct.) 1948.

The increase of prophylactic measures makes it necessary to combine vaccinations. However, problems arise with regard to the efficacy of the procedures and the intensity of the reactions. The chief problem is the competition of antigens. The role of the time factor and that of allergy must not be neglected either. The time factor determines at what time the immunity due to the prophylactic agents contained by the combined vaccine occurs and how long it will last. The allergic factor determines whether or not the reactions produced by antigens administered simultaneously are cumulative. The author made extensive trials with the combination of scarlet fever and diphtheria, and scarlet fever and whooping cough vaccines. The effect of the purified erythrogenous toxin absorbed in aluminum hydroxide, when combined with diphtheria toxoid precipitated by alum, was less effective in producing immunity than were the two vaccines separately administered, although the reaction of the combined vaccination was stronger. The results of the vaccination with the precipitated vaccine of scarlet fever and pertussis vaccine were satisfactory as regards immunity and reactions. Finally, the author devised an adequate combination of precipitated diphtheria toxoid with whooping cough vaccine, which led to good results.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF WHOOPING COUGH. JAROSLAV PROCHAZKA and ANNA TRAPLOVA, Pediat. listy **4**:189, 1949.

A short survey of the present state of therapy is presented. In particular, the use of hyperimmune serum is discussed. This serum is obtained by immunization of voluntary donors with four injections of vaccine containing 20,000,000 micro-organisms per milliliter. The total dose of serum is 100 cc. A total of 88 children were treated with the serum. Very often these children were admitted in a hopeless state. Fifty-seven of them were younger than 6 months. The mortality was 29%; half of the patients (49%) died within 48 hours after the first injection of serum. The authors consider the use of serum to be a great advance in the treatment of pertussis. However, they maintain that the introduction of obligatory prophylactic immunization will be of still greater value.

FROM THE AUTHORS' SUMMARY.

HEPATO-SPLENOMEGALY AS A RESULT OF LAMBLIASIS OF THE BILIARY TRACT. T. D. STAHLIE, Maandschr. Kindergeneesk. **19**:313 (Oct.) 1951.

Stahlie presents the case history of an 11-year-old girl with intermittent abdominal pains of almost six years' duration, in whom giardiasis of the bile passages and an enlargement of liver and spleen were found. After quinacrine (atabrine®) treatment, the symptoms disappeared

promptly and permanently. The liver and spleen regained their normal size within a fortnight after the beginning of treatment. This observation, together with those by Koumans and Beukema, strongly suggests that giardiasis of the liver is a distinct clinical entity.

FROM THE AUTHOR'S SUMMARY.

SMALLPOX VACCINATION. M-A. J. G. H. SMEETS and J. M. SOETERS, Maandschr. Kindergeneesk. **19**:325 (Oct.) 1951.

The authors discuss vaccination against smallpox in general, and a mass vaccination in Breda and its rural environs, in particular. A plea is made for compulsory vaccination of children before the age of 9 months. Some complications due to infection of the pustules by cocci and by the virus itself are described.

The hypothesis of the allergic cause of postvaccinal encephalitis is considered, and treatment of two cases with and without corticotropin (ACTH) is compared.

FROM THE AUTHORS' SUMMARY.

ANALYSIS OF EXTRA HEART TONES IN DIPHTHERIA PATIENTS WITH THE HELP OF PHONOCARDIOGRAPHY. G. M. H. VEENEKLAAS, Maandschr. Kindergeneesk. **19**:395 (Oct.) 1951.

This article discusses the possibilities of analyzing heart murmurs with the aid of phonocardiography. Some phonocardiograms of children suffering from diphtheria are described. Phonocardiographic registration often showed details which are not revealed by auscultation only.

FROM THE AUTHOR'S SUMMARY.

NERVOUS SYSTEM INVOLVEMENT IN EPIDEMIC PAROTITIS. S. E. GANZBURG, Pediatriya, January-February, 1949, p. 9.

A detailed discussion of the pathogenesis and symptomatology of nervous system involvement in epidemic parotitis among children is presented.

The opinion is expressed that epidemic parotitis should be regarded as a systemic disease with various manifestations rather than a local disease with various complications, especially since involvement of the central nervous system may occur in the absence of obvious involvement of the parotid gland.

The study is based on 61 children with mumps meningoencephalitis, ranging from 1 to 13 years of age. The onset of central nervous system involvement was observed most frequently three to four days prior to the parotid gland involvement. The specific complement fixation test was found to be a valuable diagnostic aid. In all 61 patients there was a sudden onset with high fever and severe headache. Severe and repeated vomiting (20 to 30 times a day) was present in 88.5%, whereas meningeal signs and somnolence with hypoirritability were observed in 78.6% and 67.2% respectively. Convulsions, occurring in 10%, were found to be of poor prognostic significance.

The following are the author's chief conclusions.

1. Epidemic parotitis is a systemic disease affecting the nervous system and salivary glands alike.

2. Manifestations of central nervous system involvement may occur prior to or following the onset of salivary gland involvement.

3. The clinical picture of mumps meningoencephalitis is characterized by severe, repeated vomiting and sharp headache in the presence of only mild or moderate meningeal signs; also by somnolence with hypoirritability rather than hyperirritability.

4. The severity of spinal fluid changes does not necessarily correspond to the severity of clinical symptoms.

5. The appearance of localized abdominal pain in the course of mumps meningoencephalitis indicates the presence of pancreatitis, which further helps to establish the specific nature of the disease.

BODER, Los Angeles.

TWO CASES OF FUNGUS INFECTION. E. SINGER, Chinese M. J. **66**:85 (Feb.) 1948.

In a 5-year-old Chinese girl a feverish cold with cough developed four weeks prior to hospitalization. Vomiting and general discomfort, followed by anorexia and thirst and finally headache, drowsiness, and neck rigidity, appeared over a period of five days before she was hospitalized.

The cerebrospinal fluid was clear, with 250 cells per cubic millimeter; sugar content was 48 mg. per 100 cc.; globulin reaction was negative, and no bacteria were found in the smear or culture. Repeated lumbar punctures were done, and from one of these, one month after the patient's admission to the hospital, Cryptococcus neoformans (Torula histolytica) was isolated. The patient died on the fiftieth hospital day.

This disease may be confused with tuberculous meningitis or encephalitis. C. neoformans can be cultured on blood agar. Contaminating yeasts may be detected by sugar fermentation; Cryptococcus does not produce fermentation but contaminants do, and it may be detected by its virulence in rats or mice.

The author also reports a generalized infection by an unidentified fungus in an adult.

MACDONALD, Pittsburgh.

TYPHOID MENINGITIS. NAN-GANG YU and I-LING TANG, Chinese M. J. **66**:679 (Dec.) 1948.

Six cases of typhoid meningitis are reported from Chungking. Three patients were infants under 3 months of age, the youngest 18 days. Three were adults. All died.

MACDONALD, Pittsburgh.

Chronic Infectious Diseases

THE CLINICAL IMPORTANCE OF LESIONS UNDETECTED IN A MASS RADIOGRAPHIC SURVEY OF THE CHEST. HENRY B. ZWERLING, EARL R. MILLER, JAMES T. HARKNESS, and J. YERUSHALMY, Am. Rev. Tuberc. **64**:249 (Sept.) 1951.

It has been demonstrated that in approximately 30% of persons with roentgenographic evidence of tuberculosis the abnormal densities are overlooked in a single reading of mass survey material. The importance of this observation resides in the question as to whether or not the abnormalities overlooked were clinically active tuberculosis.

In seeking an answer to this question the authors studied 1,807 photofluorograms of entering college students, which were interpreted independently 10 times by six individual readers. On one or more occasions these multiple readings brought to light 254 photofluorograms which contained abnormal shadows. The shadows in all of these were further studied in 14-by-17-in. (36-by-43-cm.) photofluorograms. Thirty photofluorograms were found in which, in the unanimous opinion of the readers, evidence of inflammatory disease was revealed. The clinical status of these "roentgenographically positive" patients was then determined by careful physical and laboratory procedures. As a result of these investigations four persons were found to have tubercle bacilli, three were "clinically active," and one other was hospitalized for seven months as a result of the survey. All seven had a positive skin reaction to the tuberculin test. In the remaining 23, the lesions were considered to be stable at the end of one year of observation.

The probability of error in interpreting the roentgenograms in mass roentgenographic surveys of the chest may be judged from the results of 10 independent readings of the 30 "roentgenographically positive" patients studied. The percent overlooked in 10 readings of each photoroentgenogram was 37.1% for the bacteriologically active cases, 42.5% for clinically active, and 30% for inactive cases.

It is suggested that the problem of error may be minimized to some extent by having the roentgenograms read independently by more than one reader.

EUGENE SMITH, Ogden, Utah.

TUBERCULOUS MENINGITIS: CORRELATION OF THERAPEUTIC RESULTS WITH PATHOGENESIS AND PATHOLOGIC CHANGES. OSCAR AUERBACH, Am. Rev. Tuberc. **64**:408 (Oct.) 1951

Tuberculous meningitis was present in 42.2% of 97 children with fatal tuberculosis. In the same series of autopsies the incidence of tuberculous meningitis in adults was 2.9% of 2,236 fatal cases.

With few exceptions, the development of tuberculous meningitis in children is secondary to a hematogenous dissemination from a primary complex. When the primary complex heals, the source of seeding is walled off and the opportunity for meningeal infection is lost. In adults tuberculous meningitis is usually associated with an acute miliary tuberculosis with extrapulmonary tuberculosis involving most often the skeletal and urogenital systems.

This difference in the pathogenesis of tuberculous meningitis may explain in part the better results obtained with streptomycin in children than in adults. In children the source of dissemination is eliminated by the healing of the primary infection, whereas in adults the meningitis is secondary to an active extrapulmonary tuberculosis which gives rise to repeated hematogenous disseminations.

EUGENE SMITH, Ogden, Utah.

STREPTOMYCIN AND PROMIZOLE IN THE TREATMENT OF TUBERCULOUS MENINGITIS IN CHILDREN. EDWIN L. KENDIG JR., FRANKLIN L. ANGELL, KENNETH BAILEY, WILLIAM M. BURCH, and LEE E. SUTTON JR., South. M. J. **44**:92 (Feb.) 1951.

Twenty cases of tuberculous meningitis in children are reported. Streptomycin or dihydrostreptomycin was administered intramuscularly in a dose of 20 to 40 mg. per pound (0.5 kg.) of body weight every 24 hours for a total of six months and intrathecally as a course of 40 injections of 25 to 50 mg. each over a nine-week period.

Thiazolsulfone (promizole®) was given, presumably orally, in a dose sufficient to maintain a blood level of 1 to 3 mg. per 100 cc. for three years. The children's ages varied from 5 months to 9 years, 12 being 1 to 2 years of age. Sixteen were colored; of these four have survived 12 months or longer since the onset of the disease. Four were white; two of them are living two years or more since the onset of the disease.

LOGAN, Rochester, Minn.

CARDIAC CONCENTRIC HYPERTROPHY IN CHILDREN WITH HYDROCEPHALUS DUE TO TUBERCULOUS MENINGITIS. JOHN L. EMERY, Arch. Dis. Childhood **26**:245 (June) 1951.

The author reports the morbid anatomical finding of concentric hypertrophy of the left ventricle in 6 of a series of 16 children dying from tuberculous meningitis treated with streptomycin. He suggests that the hypertrophy is due to hypertension of cerebral origin and is similar to the hypertension produced in animals by medullary ischemia and by the cisternal injection of kaolin.

KELLY, Milwaukee.

CONGENITAL TOXOPLASMOSIS IN AN AFRICAN CHILD. D. B. JELLIFFE, Arch. Dis. Childhood **26**:258 (June) 1951.

A case is reported in which the main features are (1) macrocephaly, possibly due to hydrocephalus, (2) radiological evidence of intracranial calcification, (3) cardiac enlargement, and (4) positive serological reactions to Toxoplasma in both the mother and the child. A diagnosis of congenital Toxoplasma infection was made. It is probable that the infection had become either quiescent or healed.

This is the first report of a case of congenital Toxoplasma infection from Africa, all previous cases having been recorded in America or Europe.

KELLY, Milwaukee.

CLINICAL OBSERVATIONS ON SOME CASES OF TOXOPLASMA INFECTION; POST-MORTEM FINDINGS IN A HUMAN AND IN ANIMALS. L. NEIDITSCHE, Schweiz. med. Wchnschr. **81**:485 (May 26) 1951.

Five cases of Toxoplasma infection are reported. The first case is that of a 4-week-premature infant, in which the prominent symptoms were drinking, weakness, severe spastic vomiting,

unclear intestinal disorder, gradually increasing toxicosis, terminal convulsions, and vasomotor disturbances. No definite symptoms of a cerebral lesion were present. The infant died at the age of 3 months. The second infant, also premature (8 weeks), was admitted with the diagnosis of hydrops fetalis and died within the first 24 hours. The spinal fluid indicated central nervous system lesions. Upon postmortem examination of both these patients Toxoplasma infection of the central nervous system was found. These findings have been reported extensively elsewhere. The third case was that of a boy referred at the age of 4 years because of a healed Toxoplasma infection. The first symptoms were noted at the age of 11 months, when the spinal fluid revealed pathological abnormalities. The course of the disease was similar to that described in the few cases of acquired Toxoplasma infection in children. There was no mental disorder, but the boy was blind. The fourth infant recovered from Toxoplasma infection which was manifested within two weeks post partum. At the age of 1½ years the child had optical atrophy and the mentality was low. The fifth infant was born of a mother in a state of severe malnutrition. At the age of 20 months the symptoms had not disappeared entirely, and the infant was mentally retarded. Another premature infant died at the age of one month with the diagnosis of hydrocephalus and encephalomeningitis. The postmortem diagnosis was Toxoplasma infection. The occurrence of Toxoplasma infection in rabbits and dogs is pointed out. The cutaneous reaction to toxoplasmin was studied in normal persons. Only in children under 2 years old (38) was the reaction negative. Later on, positive reactions were seen, and about half the adults reacted positively. It is unlikely that this indicates latent infections.

AMBERG, Rochester, Minn.

A FOLLOW-UP STUDY OF 30 CASES OF LUES CONGENITA PRAECOX FROM 2 TO 19 YEARS AFTER TREATMENT WITH ACETARSOL. GUNNAR NYHUS, Acta. pædiat. **39**:12, 1950.

During the period 1929-1946 34 infants were treated adequately with acetarsol ("spirocid") at the Department of Pediatrics, Rikshospitalet, Oslo. The total quantity of acetarsol administered varied between 5 and 80 gm. No definite grave complications occurred. Thirty of these infants came for control from 2 to 18 years after the treatment had been terminated. One of these had positive seroreactions and a positive Wassermann reaction in the spinal fluid. All the remaining patients were healthy, except two who had been exposed to traumatic brain injury at birth and had spastic paraplegia of the lower extremities. Hutchinson teeth were present in 4 of 23 possible cases. There were no skull changes. The I. Q. examination demonstrated 16 patients with normal I. Q.'s, 8 who were backward, 5 who were feebleminded and 1 idiot. Psychic defects were demonstrated in the majority of the parents of the psychically retarded children. Poor inheritance, therefore, may have been the cause of the reduced intelligence of these children with congenital syphilis. Acetarsol administered in adequate doses to infants must be regarded as an antisyphilitic as effective as other recognized agents.

FROM THE AUTHOR'S SUMMARY.

Diseases of Blood, Heart and Blood Vessels, and Spleen

A CASE OF TRANSPOSITION OF THE LARGE VESSELS IN AN ADULT WHO LIVED TO THE AGE OF 38 YEARS. C. R. MESSELOFF and J. D. WEAVER, Am. Heart J. **42**:467 (Sept.) 1951.

The case of a woman with transposition of the large vessels, interventricular septal defect, and persistent foramen ovale, who lived to the age of 38, is presented. The absence of marked cardiac enlargement and the maintenance of an adequate cardiac reserve throughout life are interesting features of the case.

FROM THE AUTHORS' SUMMARY.

VALVULOTOMY FOR THE RELIEF OF CONGENITAL VALVULAR PULMONIC STENOSIS WITH INTACT VENTRICULAR SEPTUM. ALFRED BLALOCK and RICHARD F. KIEFFER JR., Ann. Surg. **132**:496 (Sept.) 1950.

In congenital stenosis of the pulmonary valve there is a fusion of the three semilunar cusps to form a dome-like structure with a small central perforation. This condition is a mechanical disorder which can be diagnosed by available methods of study and which can be treated by direct operative attack on the valve.

The authors report their results in 19 patients, all of whom underwent pulmonary valvulotomy by the Brock technique. There were two deaths, one attributable to severe heart failure and one due to a preexisting abscess of the brain. The remaining patients are improved, and some appear to be in normal health.

BANTIN, Omaha.

RADICAL TREATMENT OF MASSIVE MIXED ANGIOMAS (HEMOLYMPHANGIOMAS) IN INFANTS AND CHILDREN. MARK M. RAVITCH, Ann. Surg. **134**:228 (Aug.) 1951.

Massive deforming angiomas which involve whole quadrants or large segments of the body have too often been considered too extensive for surgical eradication. The tumors are relatively insensitive to x-rays, and consequently a dose which is only partially effective is still likely to be massive enough to cripple the growth of the underlying tissues. The tumors tend to grow and extend under observation, and the sooner definitive treatment is undertaken the less radical it may have to be.

Radical operation for tumors such as these is justified (1) to achieve a tolerable cosmetic result, (2) to prevent ulceration and infection, (3) to forestall the occasional hematogenous infection with its severe consequences, (4) to remove a physical encumbrance, and (5) to excise the tumor before extension into neighboring tissues makes operation impossible or more disabling. There is questionable value in preserving useless, swollen limbs which are ulcerated, weeping, elephantiatic, and subject to repeated bouts of erysipelas and cellulitis. With regard to the rationale of extensive and radical operations for benign lesions, it may be fairly stated that, provided these lesions are serious and a threat to the patient, there is a sounder basis for radical surgery in these cases than in the hopelessly malignant conditions for which such operations are often performed.

In extensive mixed angioma radical extirpation appears to be the most logical form of treatment. Infants and children tolerate these extensive procedures well if properly protected with amounts of blood well in excess of that which pediatricians ordinarily consider reasonable. The author reports three cases of massive, mixed angiomas in which radical operation was performed with apparent cure.

BANTIN, Omaha.

CONGENITAL ARTERIOVENOUS ANEURISM OF RIGHT EXTERNAL CAROTID ARTERY AND POSTERIOR FACIAL VEIN WITH ABSENCE OF BRANCHES OF EXTERNAL CAROTID ARTERY. MIMS GAGE, Ann. Surg. **134**:444 (Sept.) 1951.

Congenital arteriovenous aneurysms occur much more rarely than the traumatic type. They are probably more common than the reported cases would indicate. The diagnosis of congenital arteriovenous aneurysm presents no difficulties when all signs and symptoms are present, but it may be extremely difficult if they are absent. The author emphasizes the value of arteriography. He states that in the majority of cases arteriography will reveal the anastomosis. Treatment of congenital arteriovenous aneurysm may be extremely difficult except when the disease is accessible and localized. In some cases surgical cure is questionable. The author presents in detail a case in which congenital arteriovenous aneurysm occurred between the external carotid and posterior facial vein.

BANTIN, Omaha.

AMINO ACID COMPOSITION OF HEMOGLOBINS OF NORMAL NEGROES AND SICKLE CELL ANEMICS. W. A. SCHROEDER, LOIS M. KAY, and IBERT C. WELLS, J. Biol. Chem. **187**:221 (Nov.) 1950.

In view of the recent finding that the hemoglobins of normal Negroes and of those with sickle cell anemia are unlike with respect to electrophoretic properties, the authors analyzed the two hemoglobins for their amino acid content. Chromatographic analyses were made for 17 amino acids, the results indicating that the two hemoglobins are similar with respect to amino acid content with but two exceptions. Hemoglobin from patients with sickle cell anemia contains slightly less leucine and more serine than does the normal hemoglobin.

FORBES, Dallas, Texas.

USE OF NEO-SYNEPHRINE IN PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA. GUY C. CUNNINGHAM and WILLIAM F. SCHNITZKER, J. Pediat. **37**:727 (Nov.) 1950.

Phenylephrine hydrochloride (neo-synephrine®) given intravenously will rapidly control recurrent paroxysmal supraventricular tachycardia. The initial dose is 0.1 mg.; this is increased by 0.1 mg. at 30 minute intervals to as high as 0.5 mg. Since transitory cardiac arrest may occur during administration, the drug must be given with discretion. The mechanism of action is believed to be simultaneous stimulation of the cardiac inhibitory centers, i. e., carotid sinus and aortic arch, by the sudden elevation of blood pressure. The combination of action of these two inhibitory centers is more than enough to counteract the mild stimulating influence of phenylephrine on the sinoauricular node.

MACDONALD, Pittsburgh.

POLYARTERITIS NODOSA IN INFANCY AND CHILDHOOD. DONALD B. FAGER, JOHN A. BIGLER and JAMES P. SIMONDS, J. Pediatrics **39**:65 (July) 1951.

Two cases of polyarteritis nodosa are reported, one in a boy 4 months old, the other in a 6½-year-old girl. Diagnosis in both was established at necropsy. Apparently this report brings to 54 the total number of cases of polyarteritis nodosa reported in the English literature to date.

MACDONALD, Pittsburgh.

THE COMMON HEMORRHAGIC DISEASES OF CHILDHOOD. ARMAND J. QUICK, Minnesota Med. **33**:1098 (Nov.) 1950.

Quick points out that the defect in clotting of blood in the hemophilic patient is due to a congenital lack of thromboplastinogen and that changes in the apparent severity of the disease are not caused by fluctuations in thromboplastinogen but by secondary factors, such as alteration in vascular response. The prothrombin consumption test is helpful in diagnosis. Hemophilic-like disease must be differentiated from hemophilia. This disease is caused by a factor which inhibits the platelet activator of thromboplastinogen. Hypoprothrombinemia, congenital or acquired, is a further cause of bleeding. The importance of the labile factor in the formation of prothrombin is stressed, and the depression of prothrombin synthesis by the salicylates is mentioned. The hemorrhage in thrombocytopenic purpura is due to two separate but closely related components, namely, lack of platelets and a vascular factor.

STOESSER, Minneapolis.

ANEURYSMS OF THE SINUSES OF VALSALVA: WITH REPORT OF A CASE. RICHARD E. L. FOWLER and HAROLD H. BEVIL, Pediatrics **8**:340 (Sept.) 1951.

A case of aneurysm of a sinus of Valsalva, with rupture, in a 4-year-old girl is presented. This is believed to be the youngest patient with rupture as yet reported.

Studies undertaken in an attempt to verify the diagnosis in vivo included cardiac catheterization, which yielded results compatible with a stream of arterial blood entering the venous circulation at the level of the right ventricle; arterial oxygen analysis; and oxygen uptake determination. From figures obtained by these procedures the extent of the left-to-right shunt was calculated to be about 18% of the systemic blood flow. An attempt was made to correlate the unusually benign clinical course with the results obtained from these procedures.

FROM THE AUTHORS' SUMMARY.

ELECTROCARDIOGRAPHIC PATTERNS OF NORMAL CHILDREN FROM BIRTH TO FIVE YEARS OF AGE. GERARD GROS, ARMOND GORDON, and ROBERT MILLER, Pediatrics **8**:349 (Sept.) 1951.

A study of 130 electrocardiograms obtained on 102 children in eight age groups between birth and 5 years suggested the following conclusions:

1. Electrocardiograms of the newborn infant present important variations from those seen later in life. This is especially true during the first week of life. Thereafter the countour evolves in a definite manner until the adult pattern is reached.

2. The vertical and semivertical "electric" positions were the most frequently encountered in this age range. The normal range of the P-R interval was 0.10 to 0.16 second, and of the QRS interval 0.04 to 0.08 second.

3. A Q wave is frequently absent in lead I and in all chest leads during the first week of life. Thereafter Q is generally absent in lead I and the right precordial leads, and present in lead III, aVF, and left precordial leads.

4. In the precordial leads there is a gradual change of the pattern of physiologic right ventricular preponderance, present at birth, to the pattern of left ventricular preponderance, developed after the age of 5 years. A prominent R wave, present normally at birth in V_1 and V_R, yields gradually with increasing age and with development of an S wave. Similar changes were also seen to occur in aVR.

5. The T wave is upright or diphasic in the right precordial leads and inverted in the left precordial leads for the first 24 hours of life. It gradually alters so that by the fourth day of life and thereafter it is inverted in V_1R, V_1, and V_2, and upright in V_5 and V_6.

FROM THE AUTHORS' SUMMARY.

INFECTIOUS MONONUCLEOSIS WITH PREDOMINANTLY NEUROLOGIC MANIFESTATIONS: REPORT OF CASE. W. L. HUBLER, A. A. BAILEY, D. C. CAMPBELL, and D. R. MATHIESON, Proc. Staff Meet., Mayo Clin. **26**:313 (Aug. 15) 1951.

Among the neurologic complications of infectious mononucleosis, headache and blurred vision are believed to be the commonest. There is no constant order in which the usual manifestations of the disease and the neurologic symptoms appear. In instances in which the involvement of the nervous system is severe, the changes in the blood picture tend to be delayed. Great variations exist in the duration of the neurologic disability, but rapid recovery is usual. In a review of the subject by Bernstein and Wolff it was stated that recovery was complete in 85% of cases.

In those few instances in which microscopic examination of the nervous system was carried out, a variety of lesions were observed. These included congestion, edema, and mononuclear infiltration of cranial nerve nuclei and vital medullary centers; focal degenerative changes in the Purkinje cells of the cerebellum, and perivascular cuffing and perivascular and pericellular edema in the cerebral cortex.

Because of the infrequency of convulsions in infectious mononucleosis and the diagnostic difficulties encountered, the authors report the case of a white youth aged 17 whose illness was initiated by headache, exhaustion, and slurred speech, followed in 24 hours by a generalized convulsion. From the indefinite findings in the diagnostic studies, the patient was believed to have obscure encephalitis. His condition gradually improved until, on the ninth day of illness, he again had a seizure. For the first time cervical lymph nodes were palpable. At this time blood smears and heterophile agglutination tests were ordered. On the special blood smear, leucocytoid and atypical lymphocytes were observed. In spite of the absence of pronounced lymphocytosis, this finding was considered characteristic of infectious mononucleosis. The result of the heterophile agglutination test was positive in a titer of 1:2,048 (normal 1:64). The patient was discharged 12 days later and had no residual disability when checked several months later.

The authors emphasize the important role that the special blood smear and the test for heterophile agglutinins may play in the etiologic diagnosis of an obscure encephalitis or serous meningitis.

Although the diagnosis in this case was established on acceptable criteria, the empirical use of aureomycin and corticotropin was resorted to because of the patient's extremely serious state. The successful outcome was attributed to the expected course of infectious mononucleosis with neurologic manifestations, and not to treatment.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

ERYTHROBLASTOMETRIC STUDY ON THE PARENTS OF PATIENTS WITH COOLEY'S ANEMIA. G. ASTALDI, P. TOLENTINO, and P. INVERNIZZI, Minerva pediat. **2**:361 (Aug.) 1950.

Erythroblasts from the bone marrow of 10 adults, parents of children with familial erythroblastic (Cooley's) anemia, were measured as to the size (diameter) of the nuclei and the cytoplasm. The orthochromatic and the polychromatic and to a smaller degree the basophilic erythroblasts were found to have abnormally small cytoplasms. It would thus appear that in the parents, as well as in the patients themselves, the peripheral microerythrocytosis has its origin in a microerythroblastosis. Thus, primitive genesis, rather than secondary hemolysis, is the more probable explanation of the cause of familial erythroblastic anemia.

HIGGINS, Boston.

LEUKEMOID REACTIONS IN CHILDREN. E. COSSANDI, Minerva pediat. **2**:367 (Aug.) 1950.

A case is reported of a boy of 9 months in whom a leukemoid reaction developed during the course of Staphylococcus empyema.

HIGGINS, Boston.

NEW CRITERION FOR THE DIFFERENTIAL DIAGNOSIS BETWEEN COOLEY'S ANEMIA AND JAKSCH-HAYEM-LUZET ANEMIA. F. VECCHIO, Pediatria **58**:645 (Sept.)1950.

The hemoglobin of patients with familial erythroblastic (Cooley's) anemia has a marked resistance to alkali (Kruger-Trought test), whereas the hemoglobin of three patients with anemia infantum pseudoleukaemica (Jaksch-Hayem-Luzet anemia) had a normal reaction to alkali.

HIGGINS, Boston.

LEDERER'S HEMOLYTIC ANEMIA, OF POSSIBLE FAMILIAL ORIGIN, IN AN INFANT. A. FOIS, Pediatria **58**:749 (Sept.) 1950.

A 2-month-old boy had acute hemolytic anemia (Lederer's anemia) with hemoglobinuria; he received transfusions and antibiotics and recovered from the attack. Although Lederer's anemia is usually regarded as of unknown origin, the father of this child had had two attacks of favism, with icterus and hemoglobinuria, and a sister had died at the age of 1 year of acute anemia with hemoglobinuria and fever. It would appear that the family history in this case offers a lead as to the etiology.

HIGGINS, Boston.

FURTHER STUDY ON COOLEY'S ANEMIA. L. MELE, Pediatria **58**:755 (Sept.) 1950.

The case of a child of 3½ years with familial erythroblastic (Cooley's) anemia is reported. The father of the child had had malaria and typhoid, but appeared healthy; the mother was well. The paternal grandfather had died of an undiagnosed condition characterized by intense jaundice.

HIGGINS, Boston.

ANGIOCARDIOGRAPHIC AND ANATOMIC STUDY OF TRANSPOSITION OF THE GREAT VESSELS. AGUSTIN CASTELLANOS, RAÚL PEREIRAS, and OTTO GARCIA, Arch. med. inf. **20**:149 (July, Aug., Sept.) 1951.

These authors do not agree with those who describe a constant cardiac outline in cases of transposition of the great vessels, whether the anomaly be single or multiple. They state that the diameter, situation, and direction of the great vessels is variable in different cases, and that is why the cardiac outline is also variable.

Angiocardiography gives accurate knowledge of the origin of both aorta and pulmonary artery. Thus angiocardiography makes it possible to recognize the existence of transposition of the great vessels. There are typical anatomico-angiocardiographic forms or variations of transposition of the great vessels, which include all types described up to the present.

For the transposition of the great vessels, angiocardiography is the best diagnostic method, on account of its rapidity, innocuousness, and easy performance.

FROM THE AUTHORS' SUMMARY.

ANOMALIES OF THE VENA CAVA: ANATOMICAL TYPES: ROENTGENOLOGIC DIAGNOSIS. AGUSTIN CASTELLANOS, Arch. med. inf. **20**:191 (July-Aug.-Sept.) 1951.

The author reviews the material on anomalies of the superior vena cava and gives an anatomicosurgical classification of these anomalies with the object of pointing out those cases in which the abnormal vena cava can be ligated or sectioned with resultant improvement in the symptomatology without there being any disturbing effects or aggravation.

Classic angiocardiography, and especially its modification, cavography, is the best existing method for the diagnosis of the anomalies of the inferior and the superior vena cava.

The abdominal venous system, which ends at the right auricle, also has anomalies, and the same points hold true as for anomalies of the superior vena cava: Angiocardiography and cavography are the most graphic methods, the surest, and the most innocuous for the anatomic diagnosis.

The cardiovascular roentgenologist must be familiar with the embryology and the existence of the different anatomic types of anomalies of the superior and the inferior vena cava in order to be able to make the diagnosis with exactness.

FROM THE AUTHOR'S SUMMARY.

ACUTE HEMOLYTIC ANEMIA (LEDERER'S) WITH INFECTIOUS MONONUCLEOSIS. ANTON S. PETRIDES, Monatsschr. kinderh. **97**:56 (June) 1949.

Infectious mononucleosis (Pfeiffer's lymph node fever of children) is very rarely accompanied with disturbances in the erythropoietic system, which, among other criteria, serves to distinguish it from leukemia. The author reports the case of a 3-year-old white boy with infectious mononucleosis who also showed an acute hemolytic anemia in the course of the disease. Red cell counts dropped to as low as 1,480,000, hemoglobin to 27%; reticulocytes rose as high as 193%. Anisocytosis, macrocytosis, and immature red cells were seen in the peripheral blood. The bone marrow also showed increased erythropoiesis. Red cell fragility was normal.

Another interesting feature of the case was an early pulmonary lymphadenopathy before the generalized lymphadenopathy appeared. It gave rise to a spastic cough, which is often difficult to differentiate from pertussis, as the blood pictures are sometimes similar.

The author believes that this type of anemia fits into the group of Lederer's anemia. Examination at two, three, and six months after onset of the disease showed normal blood pictures.

HARTENSTEIN, Chicago.

REGENERATIVE REACTIONS IN ANEMIA DUE TO INFECTIONS IN CHILDHOOD: CONSIDERATIONS OF THE PATHOGENESIS OF INFECTIOUS ANEMIAS. K. H. SCHÄFER and I. BOENECKE, Ztschr. Kinderh. **65**:550, 1948.

By studying the bone marrow and peripheral blood, the authors attempt to determine the pathogenesis of infectious anemias—whether it is primarily an aregenerative process, a maturation arrest, or a frustrated overproduction. They conclude that all processes may be involved, depending upon duration and severity of the disease and the nutritional state of the diseased person, but independent of the age of the patient or the nature of the infection. Because of the poor nutritional state of children in Germany at present, the aregenerative type seems to predominate. The authors feel that toxicoinfectious influences and iron deficiency are both causatively involved, but that generally the iron deficiency will be more important in infections of long duration or preceding alimentary iron deficiency. The therapy of choice is blood transfusion. Iron therapy should be employed only in cases with low color index and may even then be of poor success in the presence of an infection.

GLASER, Chicago.

SOME VIEWS ON THE TECHNIQUE OF HEMOGLOBIN DETERMINATION. P. KARLBERG and B. VAHLQUIST, Svenska läk.-tidning. **45**:1301 (July 2) 1948.

A comparison of the different types of methods for hemoglobin determination, with consideration of the time consumed for each test, is presented. It is concluded that a photoelectric cell colorimeter is most suitable for hospitals and the Sicca method the best for practitioners. For a rough estimation of the hemoglobin value, the simple gravimetric method of Phillip and van Slyke is recommended.

WALLGREN, Stockholm, Sweden.

"AMINOPTERIN" AND EXCHANGE TRANSFUSIONS IN ACUTE LEUKEMIA. C. G. BERGSTRAND and B. VAHLQUIST, Svenska läk.-tidning. **45**:2397 (Dec. 10) 1948.

Bergstrand and Vahlquist report the first two patients in Sweden with acute leukemia who were treated, with temporary satisfactory effect, with 4-aminopteroylglutamic acid ("aminopterin") combined with exchange transfusions.

WALLGREN, Stockholm, Sweden.

THROMBOSIS OF THE VENA CAVA SUPERIOR. A. K. A. GIJSBERTI HODENPIJL, Maandschr. kindergeneesk. **19**:310 (Oct.) 1951.

The article describes the case of a girl of 1½ years, who showed symptoms of dyspnea, cyanosis, and edema of the upper part of the body, which were thought to be due to a mediastinal tumor. Later, however, it was found that thrombosis of the superior vena cava had occurred. The child recovered.

FROM THE AUTHOR'S SUMMARY.

THE HOMOZYGOTIC FORM OF NUCLEAR ANOMALIES OF PELGER-HUET. N. HAVERKAMP BEGEMANN and A. VAN LOOKEREN CAMPAGNE, Maandschr. kindergeneesk. **19**:338 (Oct.) 1951.

In a girl 2½ years old, examined for epilepsy, an anomaly of the nuclei of the granulocytes was observed. Photographs of these cells are given. As the nuclei closely resembled those seen in rabbits with the homozygous form of Pelger-Huet's hereditary anomaly, and as the heterozygous form was found in both parents, the authors believe they are justified in assuming that they have found here the homozygous form of the anomaly in man, which had not previously been described

Some peculiarities in the pedigree require further investigation.

FROM THE AUTHORS' SUMMARY.

TERMINAL CYANOSIS IN A PATIENT WITH AN OPEN DUCTUS BOTALLI. C. BRUINS, Maandschr. kindergeneesk. **19**:368 (Oct.) 1951.

Bruin describes the symptoms and pathophysiology of a girl who died at the age of 4 years. The postmortem diagnosis was patent ductus arteriosus with vascular changes in the lungs which caused terminal cyanosis and reversal of flow through the ductus, with failure of the right side of the heart.

FROM THE AUTHOR'S SUMMARY.

TWO PATIENTS WITH THE SYNDROME OF LETTERER-SIWE. J. H. VAN BOLHUIS and W. NOLEN, Maandschr. kindergeneesk. **19**:374 (Oct.) 1951.

Two cases of Letterer-Siwe's syndrome are presented. The first child died at the age of 20 months. The second one was still alive at the age of 25 months after 15 months of treatment. In this child the condition had passed from the acute phase with fever, enlarged lymph nodes, splenomegaly, and osseous and cutaneous manifestations, into a chronic phase with development of symptoms resembling the syndrome of Hand-Schüller-Christian. Histological findings of one of the bone lesions verified this opinion. Intravenous treatment with nitrogen mustard, aided by antibiotic treatment, is described.

FROM THE AUTHORS' SUMMARY.

Diseases of Nose, Throat, and Ear

AN ANALYSIS OF 500 CASES OF HEARING DISABILITY. HAYES A. NEWBY and DOROTHY MUNZ MOLYNEAUX, J. Speech and Hearing Disorders **16**:213 (Sept.) 1951.

In this analysis 292 females ranging in age from 6 to 89 years with a median of 45, and 208 males ranging from 6 to 81 years with a median of 46 were classified under 10 types of hearing loss. Comparison was made with referral diagnoses of nerve deafness, otosclerosis, and mixed deafness. Nerve deafness may be diagnosed on a basis of an increasing loss from frequency to frequency in both bone and air conduction and with relatively poor speech sound discrimination. Diagnosis of otosclerosis may be based on a flat or slightly rising pure tone audiometric pattern, relatively normal bone conduction, and relatively good speech sound discrimination.

PALMER, Wichita, Kan.

THE EFFECT OF SPEECH TRAINING ON SILENT READING ACHIEVEMENT. MORRIS VAL JONES, J. Speech and Hearing Disorders **16**:258-263 (Sept.) 1951.

In this study 61 pairs of third grade pupils from 10 classrooms of the Santa Ana, Calif., city schools were matched individually for chronological age, mental age, silent reading achievement, sex, and teacher. All were normal in vision, auditory acuity, and speech. Members of the experimental group were taken from their regular classrooms for a series of 36 speech improvement lessons, each half an hour in length. The lessons were intended to develop speech sound discriminations, skill in speech production, etc. There was a significant increase in silent reading achievement and paragraph comprehension in the experimental group. The boys were below the girls at both the beginning and the end of the study. PALMER, Wichita, Kan.

Diseases of the Lung, Pleura and Mediastinum

HYDATID CYSTS OF THE LUNG IN INFANCY. J. GARRIDO LESTACHE Y DIAZ and J. GARRIDO LESTACHE Y CABRERA, Acta pediat. españ. **88**:431 (April) 1950.

The authors suggest that if all cases of echinococcic cysts in Spain were reported, a map could be made showing distribution and a large variety of animal hosts responsible for this disease. Cases have already been reported in which the infectious agent was carried by dogs, cats, oxen, sheep, pigs, horses, goats, etc.

All patients studied by the authors were children at Children's Hospital in Madrid. In the largest number, cysts were localized in the liver, but in others these were identified in the lungs, bones, muscles, and rarely in the cerebrum. One patient, a girl of 3 years, had the multiple form in the liver and right lung. One cyst was localized in the thyroid gland.

The authors discuss the port of entry and the means of travel to various parts of the body. In the pulmonary cases, the symptoms are very similar to those of pulmonary tuberculosis with certain very outstanding differences. In uncomplicated cases of hydatid cyst there is no fever. Later complications and infections superimposed, however, may cause fever and simulate tuberculosis.

Dyspnea is dependent upon the size of the cyst and may become very marked if a large area is involved. Hemoptysis is the symptom which should be most revealing, as children in good health rarely have this and, indeed, rarely have pulmonary tuberculosis. However, a child in apparently good health may have a pulmonary hemorrhage due to hydatid cysts.

The cough is not very marked; there is some expectoration in older children, but when the cyst breaks there will be a suffocating cough with mucosanguineous discharge and large amounts of turbid fluid. It is not always necessary to find a clear egg-white-like fluid and a hard rock-like mass, but sometimes these may be found along with unruptured vesicles and the scolex which confirm the diagnosis.

The clinical symptoms vary from a series which simulate pleuritis to those of tuberculosis or tumor of the lung.

Exploratory aspiration may help the diagnosis but is not without danger both immediately to the patient and by spread to contiguous parts of lung tissue.

Microscopic investigation of gastric contents sometimes reveals fragments of the cuticular membrane or excolex which may exist when an open cyst is present, and its contents coughed up and then swallowed.

Eosinophilia may be noted in most cases, but it must be remembered that it is also present in a number of other maladies.

The reaction of Weinberg-Parvu is positive in 90% of the cases but a positive Weinberg-Parvu reaction has occasionally been noted in gangrene and tumor of the lungs. Other tests, such as the intradermal test of Casoni, and that of Pontana, are slightly less accurate.

The authors feel that the x-ray findings are most important, especially in the lung, and give various details of roentgenographic findings. Most significant is the oval shadow of the cyst on inspiration and its change to a round shadow on expiration.

The treatment is preventive: first, treatment or destruction of animals having the disease; and second, prevention of children's contact with animals in areas known to be infested with the Echinococcus.

Surgery is the method of choice, and in a small cyst one should wait to determine whether it will increase in size or not. Frequent roentgenograms are necessary when the cyst becomes adherent to pleura; surgical intervention is easiest. High voltage x-ray therapy has been suggested to sterilize the cyst. Reports of this type of treatment have been published by Garcia, Ortiz, and Galvez, but the authors have had no experience with it. Medical treatment by injections, etc., has proved ineffective.

ALLEN, Santa Fe, N. M.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

THE TREATMENT OF INGUINAL HERNIA IN INFANTS AND CHILDREN. WILLIS J. POTTS, WILLIAM L. RIKER, and JAMES E. LEWIS, Ann. Surg. **132**:566 (Sept.) 1950.

The treatment of typical inguinal hernia in infants and children is surgical removal of the sac without elevating the structures of the cord and without any plastic repair of the muscles or fascia of the inguinal region. Approximately 600 hernias in infants and children were operated upon according to this method. Follow-up studies of 100 infants and 100 children revealed one questionable recurrence, in a 3-year-old child.

BANTIN, Omaha.

ACUTE APPENDICITIS IN CHILDREN. WILLIAM G. ABEL III, and PHILIP D. ALLEN, Ann. Surg. **132**:1093 (Dec.) 1950.

The authors reviewed 1,165 cases. The material for this study was taken from the Children's Surgical Service, Bellevue Hospital.

The high death rate from spreading peritonitis in the infant is well known. The following factors are thought to play an important role: (1) the increased time elapsing from onset of symptoms to operation as compared to the older age groups, (2) the inability of the underdeveloped omentum to wall off perforations, and (3) the greater difficulty in establishing and maintaining fluid, protein, and electrolyte balance in the young infant. Other variables which must be considered to influence mortality are (*a*) hours from onset of symptoms until admission, (*b*) hours from admission until operation, (*c*) whether catharsis has been given, (*d*) age of patient, (*e*) severity of pathologic changes in the appendix, (*f*) whether chemotherapy or antibiotics are administered, and (*g*) the surgical technic employed.

BANTIN, Omaha.

RUPTURED OMPHALOCELE AND JEJUNAL ATRESIA. PAUL F. FOX and JAMES E. BRENNAN, Ann. Surg. **133**:123 (Jan.) 1951.

The authors report an unusual case. Two rare anomalies, ruptured omphalocele and jejunal atresia, were present in a newborn infant. Two separate surgical procedures were performed to correct these anomalies. Recovery was satisfactory, and development of the infant is apparently progressing normally.

BANTIN, Omaha.

RETROPERITONEAL TERATOMAS IN INFANCY AND CHILDHOOD. ERNEST E. ARNHEIM, Pediatrics **8**:309 (Sept.) 1951.

On the basis of 44 cases, Arnheim reviews histogenesis, pathologic and clinical features, diagnosis, and treatment of retroperitoneal teratomas in infancy and childhood. Two cases of benign retroperitoneal teratoma with recovery and one case of maligant retroperitoneal teratoma with subsequent death are presented.

Retroperitoneal teratomas were usually noted in girls under the age of one year as large, left-sided, abdominal tumors extending into the lumbar region, rarely causing symptoms, and revealing areas of ossification on roentgen examination.

In this series 6.8% of the teratomas had undergone malignant changes; 29.5% of the tumors were not operated upon and were described at autopsy.

Successful treatment of retroperitoneal teratomas was dependent upon early operation, careful operative technic through a liberal transperitoneal incision, and adequate preoperative and postoperative management. The operative mortality was 29%.

The histologic features constituted an important factor in prognosis: 10 patients with benign retroperitoneal teratoma in infancy or childhood were well for periods of over one year after operation; no cure of malignant retroperitoneal teratoma has been reported in this age group.

FROM THE AUTHOR'S SUMMARY.

ATRESIA OF THE INTRAHEPATIC BILE DUCTS. EDWARD H. AHRENS JR., RUTH C. HARRIS, and H. EDWARD MAC MAHON, Pediatrics **8**:628 (Nov.) 1951.

Case histories of four patients with atresia of the intrahepatic interlobular bile ducts are reviewed. Three of the four also had anomalies of the extrahepatic bile ducts. All had secondary biliary cirrhosis. The course of disease was distinguished by a relatively long life span, all patients surviving more than three years and one remaining alive at five years. Generalized skin xanthomatosis occurred in all patients, together with a marked and characteristic elevation of the serum lipids. No pathologic evidence could be found to suggest that intrahepatic bile ducts had developed and then become obliterated. It is concluded that absence of interlobular bile ducts is a developmental anomaly and that the embryologic development of biliary epithelium is normally independent of the growth of hepatic trabeculae.

FROM THE AUTHORS' SUMMARY.

HEAT PROSTRATION IN FIBROCYSTIC DISEASE OF THE PANCREAS AND OTHER CONDITIONS. WALTER H. KESSLER and DOROTHY H. ANDERSEN, Pediatrics **8**:648 (Nov.) 1951.

During the heat wave in August, 1948, 10 patients with heat prostration were seen at the Babies Hospital in New York City within a period of one week. The clinical picture was manifested by sudden onset, fever, vomiting, irritability, marked dehydration, and signs of circulatory collapse in the absence of any obvious clinical evidence of acute infection. Five of these ten children, surprisingly, were patients for whom the diagnosis of cystic fibrosis of the pancreas had been established during previous admissions to Babies Hospital. All five patients were considered to be doing well at the time of onset of the heat wave. Treatment consisted essentially of adequate hydration, oxygen, and cooling sponge baths. The response was prompt in four of the patients with fibrocystic disease; the temperature returned to normal within 48 hours. The only patient with fibrocystic disease who died was admitted to the hospital wrapped in a woolen blanket despite a body temperature of over 107 F. He died one hour after admission. Of the patients who did not have cystic fibrosis of the pancreas, one had congenital heart disease, two had recently undergone surgery of the gastrointestinal tract but were in no acute distress prior to the hot weather, and one had cerebral hyperplasia. As a group their response to therapy was less prompt, and their symptoms were only alleviated at the end of the heat wave. Two additional patients with heat prostration were seen in the succeeding two summers. Both of these were children with fibrocystic disease.

FROM THE AUTHORS' SUMMARY.

SPLANCHNICECTOMY FOR PANCREATIC FIBROSIS: ANALYSIS OF RESULTS IN 24 PATIENTS. W. B. AYERS, DANIEL STOWENS, ALTON OCHSNER, and R. V. PLATOU, Pediatrics **8**:657 (Nov.) 1951.

Based on the rationale that splanchnicectomy might interrupt a viscerovisceral autonomic reflex arc responsible for bronchospasm and bronchorrhea, this operation has been performed on 24 infants and children with mucoviscidosis, most of whom were poor operative risks. Three of them died at or soon after operation, and six others have died at intervals of from 2 to 12 months postoperatively. Of the remaining 15, manifestations are essentially unchanged in 5 and equivocally ameliorated in 6. No information could be secured concerning the late effects in one child. Three patients may have been materially benefited by the procedure.

FROM THE AUTHORS' SUMMARY.

BENIGN HYPERTROPHIC PYLORIC STENOSIS WITH RADIOGRAPHIC ILLUSTRATIONS. DIANA J. O'CONNOR, Clin. Rep. Adelaide Child. Hosp. **2**:56 (May) 1951.

Pyloric stenosis is discussed and the roentgenographic findings described.

McGUIGAN, Evanston, Ill.

FETOR HEPATICUS. ERNST FREUDENBERG, Ann. pædiat. **173**:80 (Aug.) 1949.

"Fetor hepaticus" is caused by mercaptan, which is formed from methionine. Ingestion of methionine by patients with liver affections (2 to 5 gm. in children) causes excretion of mercaptan in the expired breath. The mercaptan smell was less intense in persons with healthy livers who were given the same dose of methionine.

FROM THE AUTHOR'S SUMMARY.

THE TREATMENT FOR VOMITING IN INFANTS BY "THICK FEEDINGS." G. CHIARI, Lattante **22**:403 (July) 1951.

Carob powder was used to thicken the feedings given to 15 infants with vomiting. The treatment was adequate in controlling the vomiting in nine of the milder cases. In the other six cases, "short-wave" therapy was also necessary to get a satisfactory recovery. The combination of thick feedings and Marconi therapy is recommended for infants with pyloric stenosis or pylorospasm.

HIGGINS, Boston.

PYLORIC DISEASE OF INFANCY—ETIOPATHOLOGY AND TREATMENT. EDUARDO MORANTE SERNA, Acta pediat. espan. **9**:281 (March) 1951.

Pyloric disease is a disease of the first three months of life. Anatomically there are two varieties—one with tumor mass at the pyloric end of the stomach, and the other without definite tumor mass. Clinically, it is often difficult to distinguish between the two, and the treatment is the same—medication and diet, which in some cases must be followed by surgery.

The pathogenesis appears to be related to certain developmental lesions in the local area, such as dysplasia, inhibition of proper development, and persistence of the mesenchymal state, with insufficient involution. Such anatomical anomalies are not sufficient to produce the illness; there is also a spastic predisposition or diathesis, such as neuropathy, vegetative dystonia, or lack of vitamins E and B.

In the hypertrophic variety with tumor, both organic and functional factors are responsible, whereas in the simple form only the functional factor is involved. If effective treatment is possible without surgery, "what matters the presence of a tumor?" A tumor of this type has been found on autopsies of children who died of other conditions six months to three years after they were cured of pyloric disease (without surgery).

The number of patients relieved by diet and medication, and by surgery are about the same. Serna gives a detailed discussion of diet and medication commonly used in Spain. The drugs

are of three classes: (1) those with action on the vegetative nervous system; (2) those with action on the central nervous system; (3) those causing a local anesthesia. The variety of drugs used is quite large within these groups.

Ultraviolet light and diathermy have also been used with not too great success, but with the idea of providing local heat and relaxation of the spasm. The author considers large doses of vitamins E and B very efficacious, in that they help to retain fluids, diminish the neuropathy, and favor rapid recuperation by the infant.

The surgical technique is also discussed at length. In simple cases conservative treatment may be used. If after seven days the symptoms persist, operation should be performed. The child in coma or incipient coma should be treated surgically; the child who vomits blood and those in whom there is a tendency to dehydration should be subjected to surgery.

Social and economic conditions in the home may necessitate early surgical intervention because of failure of parents to follow instructions in diet and medication. The condition should never require an operation after the third month, as the symptoms disappear.

When operation is properly done, the mortality is very low. The operation, pyloromyotomy, is the same, whether a tumor is present or not.

ALLEN, Santa Fe, N. M.

CHOLANGIOPATHY IN CHILDHOOD. HUMBERTO J. NOTTI, ABRAHAM GRINFELD, and JUAN TOMARCHIO, Rev. chilena pediat. **22**:285 (July) 1951.

The authors report 10 cases of disease of the gall bladder and bile ducts seen during the last 13 years at the "Emilio Civit" Hospital. These 10 cases included three of cholelithiasis, one of cholecystitis, one of choledocholithiasis with purulent cholecystitis, three perforations of the gall bladder during typhoid fever, one congenital malformation of the bile ducts, and one cholecystatony.

In many cases of cholelithiasis there are concomitant liver changes that can be demonstrated either by biopsy or by liver function tests.

The authors review very thoroughly the different clinical manifestations of biliary calculi, their pathogenesis and treatment. The basis for the differential diagnosis of jaundice in the newborn period is analyzed.

FROM THE AUTHORS' SUMMARY.

ENTEROCOLITIS IN THE INFANT: USE OF STREPTOMYCIN IN TREATMENT. FRANCISCO PEDRAZA FULLER, Pediat. Américas **7**:392 (Sept.) 1949.

Thirty-six cases of acute enterocolitis in infants are studied from the following points of view: clinical, etiologic, epidemiologic, and therapeutic. Only two children were breast fed. A hospital epidemic is described which was traced to incorrect use of a rectal thermometer. Stool cultures showed Salmonella in 64% of the cases. Proteus was found in 28%, associated in one case with Shigella and in two with Salmonella. In five cases Shigella paradysenteriae (Flexner's bacillus) was identified. In one child the blood culture yielded Salmonella kauffmannii.

For only one patient was streptomycin used parenterally, 50 mg. every four hours. In all the other patients streptomycin was administered orally, 25 mg. every three hours for the first 24 hours and 50 mg. later for children less than 6 months old. For older patients a dosage of 50 mg. every 3 hours was used from the beginning. The mortality rate was less than 3%. The best results were obtained in patients with Salmonella or Proteus infections.

DE LA TORRE, México City, D. F., Mexico

ZYMOGEN AREAS IN HUMAN PANCREAS. W. BURKL, Wien. klin. Wchnschr. **61**:264 (May 6) 1949.

It had been shown that in animals starving several days enlarged acinar cells surrounded the islands of Langerhans and that these cells were filled with eosinophile granules. Such areas were demonstrable in three cases, one of which was that of an 8-year-old girl.

AMBERG, Rochester, Minn.

ESSENCE AND SIGNIFICANCE OF NEW SERUM REACTIONS. RICHARD BAUER, Wien. klin. Wchnschr. **61**:370 (June 17) 1949.

The magnesium chloride test, a colloid gold test, the cephalin cholesterol test, and the thymol turbidity test were studied in some cases of liver disease, with addition of various electrophoretically prepared protein fractions. It is concluded that human serum contains favoring and inhibiting substances.

AMBERG, Rochester, Minn.

DUPLICATION OF SMALL INTESTINE. H. HARTL, Wien. klin. Wchnschr. **63**:795 (Oct. 19) 1951.

A 15-year-old boy had, since early childhood, occasional spasmodic abdominal pains, which were not relieved by an appendectomy at 3 years of age. On exploration, a duplication of the small intestine, measuring 35 cm., was found; this was removed together with a portion of the small intestine. The mucosa of the duplication was like stomach mucosa. A callous peptic ulcer was located in the blind end of the duplicate intestine.

AMBERG, Rochester, Minn.

CYSTIC FIBROSIS OF THE PANCREAS. R. PEETERS, Acta pædiat. belg. **3**:167 (Pt. 3) 1949.

The blood groups and antibodies of a patient who suffered from fibrocystic disease of the pancreas were investigated and also those of his parents. Two other children of the same parents had died, presumably of the same condition, and a third showed growth disturbances and bronchiectasis. The author concluded that no etiologic connection existed between Rh-incompatibility and this disease.

GLASER, Jerusalem, Israel.

DIGESTIVE AND NUTRITIONAL DISTURBANCES. C. CHMELO and L. ORICH, Paediat. danub. **5**:305 (June) 1949.

Among the 2,349 children under 2 years of age admitted to the department of pediatrics of Bratislava University in 1946, there were 632 with diarrhea, an incidence of 26.9%. Of 147 in whom no complication was associated with the disease, 9 died (6.1%). In 290 patients different complications developed; 25 (8.6%) of these died. There were 118 patients with grave infantile diarrhea (toxicosis), of whom 34 died, i. e. a 28.8% mortality rate. The severer the disease, the longer the recovery. Good results were achieved with a diet of carrot soup.

FROM THE AUTHORS' SUMMARY.

SUPPORTING THERAPY WITH EMETINE IN SUPPURATIVE PERITONITIS IN CHILDREN. V. TOSOVSKY and V. HOLUB, Pediat. listy **6**:217 (No. 4) 1951.

In 30 children with perforated gangrenous appendicitis, phlegmonous appendicitis, or peritonitis, subcutaneous injections of 0.02 to 0.03 gm. of emetine hydrochloride was administered according to Melchjor's method (Turkey). Other treatment (antibiotics, infusions, transfusions) was continued as usual. This is a preliminary report but the authors consider that the effect of their therapy is beneficial. Emetine has a stimulating, bactericidal, and analgesic effect and a soothing effect on peristalsis.

FROM THE AUTHORS' SUMMARY.

CASE OF TUBERCULOUS HEPATITIS. K. CHOREMIS and N. NINIOS, Acta Soc. pediat. hellen. **2**:145 (July-Aug.) 1948.

A 14-year-old boy had a high temperature, hepatomegaly, pain in the right hypochondrium, and severe anorexia. After failure of two courses of penicillin and after persistence of the symptoms for seven weeks, laparotomy was performed. The liver was found dark and covered with yellowish spots and small nodules. Biopsy revealed the presence of numerous tubercles in the process of caseation.

A blood culture showed presence of Mycobacterium tuberculosis. After two months' treatment with a total of 45 gm. of streptomycin, there was a marked improvement in the general condition and a decrease in the size of the liver. The tuberculin skin test, which was negative

up to 1 mg. of old tuberculin as late as four weeks after the onset of the treatment, became positive later. This observation may be related to the important rôle of the liver in the mechanism of allergy.

DOXIADIS, Sheffield, England.

OCCLUSION OF THE SMALL BOWEL. P. DENYS, Maandschr. kindergeneesk. **19**:286 (Oct.) 1951.

Brief descriptions are given of six cases of occlusion of the small bowel. Two patients with congenital aplasia were treated by latero-laterale anastomosis, with one death and one recovery. One patient had a congenital lymphatic cyst of the mesentery with secondary occlusion. The cyst, with part of the intestine, was extirpated. After three days the patient died of peritonitis. One case of meconial ileus, appeared five weeks after birth in a child suffering from fibrosis of the pancreas. The patient died during operation. There were two cases of intussusception of a very particular type, following an umbilical aperture and an intestinal perforation. The two patients recovered, one after exteriorization of the intussusception and closure of the perforation, the other after resection of the cecum, appendix, and intestinal segment, with ileocolic anastomosis.

The determination of the obstruction level and the diagnosis of subocclusion may present serious difficulties. In this last instance a pain syndrome may be the major sign. The resistance of babies with a sound organism to undernourishment and to operative shock is very high. Provided that one uses large doses of antibiotics and parenteral feeding, apparently desperate situations may be resolved.

FROM THE AUTHOR'S SUMMARY.

FAMILIAL LIVER DISEASE WITH GALACTOSEMIA. P. K. DE HAAS, Maandschr. kindergeneesk. **19**:304 (Oct.) 1951.

Eight newborn babies in one family died shortly after birth with signs of liver disease, caused by galactose. A similar history in the family of her parents was recounted by the mother.

De Haas found no abnormalities in the newborn babies immediately after birth. The first symptoms came only after a few days. The children showed icterus, a progressive enlargement of the liver, and a hemorrhagic diathesis in the urine albumin and galactose were found. Galactose was also found in the blood.

FROM THE AUTHOR'S SUMMARY.

INTUSSUSCEPTION. A. C. MA, S. Y. AN, and C. C. SHEN, Chinese M. J. **69**:239 (May-June) 1951.

More than half of the 28 patients with intussusception were over 10 years old. The younger patients manifested classic symptoms of the acute disorder. The older patients, some of whom had chronic intussusception, all complained of pain and demonstrated a palpable abdominal mass but, in several instances, no vomiting and/or no bloody stools.

MACDONALD, Pittsburgh.

Nervous Diseases

INTELLECTUAL AND EMOTIONAL MAKEUP OF THE EPILEPTIC. FREDERICK T. ZIMMERMANN, BESSIE B. BURGEMEISTER, and TRACY J. PUTNAM, A. M. A. Arch. Neurol. & Psychiat. **65**:545 (May) 1951.

Intelligence and personality of epileptic children were studied in connection with a clinical etiologic classification of the epileptic seizure. It was found that such a classification based on commonly accepted clinical seizure types revealed differences in intelligence and personality in these groups. Patients with petit mal showed the least deviation in personality and the highest I. Q., those with the severer type of seizures showing more marked changes.

MCGUIGAN, Evanston, Ill.

BACILLUS PROTEUS ABSCESS OF CEREBELLAR LOBE OF OTOGENIC ORIGIN. W. R. CHAMBERS and W. CLARK, A. M. A. Arch. Otolaryng. **54**:179 (Aug.) 1951.

Chambers and Clark report the case of a boy aged 16 with cerebellar abscess and subdural abscess in the posterior fossa, of otogenic character and due to a Proteus vulgaris infection. Cerebellar abscess from this source is rare, as is any brain abscess due to this infectious agent. In either of these circumstances prognosis has been poor in the past.

The patient was subjected to three operations and was discharged after 78 days in the hospital, having received 53.5 gm. of streptomycin, as well as 17,350,000 units of penicillin, 2,000 mg. of aureomycin, 55,750 mg. of chloramphenicol, 3.5 gm. of sulfadiazine, and 4 gm. of eskadiazine® (a 10% [W/V] aqueous solution of microcrystalline sulfadiazine). Two months after discharge he was able to ride a bicycle without difficulty, and all his residual neurological signs had improved.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

THE DIAGNOSIS AND TREATMENT OF MENINGITIS. WILLIAM J. KERR JR. and EDWARD B. SHAW, California Med. **73**:325 (Oct.) 1950.

Treatment of meningitis no longer consists in administration of antimeningococcal serum and awaiting the results. Today there is at hand an ever-expanding armamentarium of drugs effective on various bacteria, rickettsia, and some of the larger viruses. The skillful use of these singly or in combination offers an excellent prognosis in most forms of bacterial meningitis. Tuberculous meningitis continues to present a poor outlook, but this has been improved with more intensive therapy. More effective agents are needed in the treatment of this disease.

"Shotgun" therapy may be indicated in critically ill patients prior to accurate bacteriological diagnosis; it is more important, however, that therapy should include an effective agent or combination of agents than that an attempt be made to determine in advance the most potent form of specific therapy. Partially treated purulent meningitis may be confused with aseptic meningitis. There is at present no effective therapeutic agent for the viral meningitides, but the prognosis is favorable in most of these diseases without specific therapy.

PRYOR, Redwood City, Calif.

THE ADAPTATION OF ELECTROENCEPHALOGRAPHY TO MEDICINE. CHARLES L. YEAGER, California Med. **73**:350 (Oct.) 1950.

Electroencephalography is a valuable aid in diagnosis and prognosis of diseases affecting the brain. It has definite limitations. Abnormal electroencephalograms are either paroxysmal or nonparoxysmal. Both of these changes may be generalized or focal. Epilepsy is primarily associated with paroxysmal activity. Electroencephalography aids in the diagnosis and in determining the severity, course, and response to treatment. Nonparoxysmal activity, although less specific in pattern, indicates either generalized or focal pathologic change or some alteration of the normal structure of the brain. Nonparoxysmal activity may give supportive evidence referable to conditions, systemic or intracranial, which disturb the state of consciousness.

PRYOR, Redwood City, Calif.

HEREDOFAMILIAL CEREBELLAR ATAXIA WITH SPASTIC PARALYSIS AND SPINAL MUSCULAR ATROPHY. EDWIN DENNIS KILBOURNE, J. Nerv. & Ment. Dis. **109**:409 (May) 1949.

Two cases are presented, those of a brother and sister aged 25 and 29 years, respectively. Symptoms began at age 5 years in the brother and at 13 years in the sister. The disease in the brother included the pyramidal tract and the cells in the anterior horn, with the lower extremities principally affected. The sister suffered primarily from cerebellar symptoms with ataxia and vertigo. In neither of the patients was there any sensory disturbance or loss of tendon reflexes.

Although the symptoms bear some resemblance to Friedreich's ataxia, they have too many varying features to place them in any known classic syndrome.

JAHR, Omaha.

HALLERVORDEN-SPATZ DISEASE AND DYSTONIA. M. G. NETSKY, D. SPIRO, and H. M. ZIMMERMAN, J. Neuropath. & Exper. Neurol. **10**:125 (April) 1951.

Eight cases of Hallervorden-Spatz disease with autopsy are recorded in the literature. The authors add two pathologically verified cases to that number. In one, the clinical syndromes of dystonia musculorum deformans and Friedreich's ataxia were present. In the other, no clinical evidence of neurologic disorder was obtained, demonstrating that the pathologic picture may be present in a patient with no clinical signs or symptoms.

A review of the reported cases of Hallervorden-Spatz disease reveals that they are characterized pathologically by deposition in the globus pallidus and the pars reticularis of the substantia nigra of relatively large amounts of a pigment containing iron, fat, and some calcium. The pallidal cells are altered or destroyed. Usually, the striatum is involved, but to a less degree. Variable changes are seen also in the cerebellum and the cerebral cortex. Demyelination of the involved areas may or may not be present.

The clinical features common to most cases are a positive family history, presence of hereditary stigmas, onset between the ages of 6 to 14 years, presence of rigidity and/or involuntary movements, absence of sensory changes, progressive mental deterioration, and gradual decline over a period of about 12 years.

The possibility that an alteration of iron metabolism is the defect present in dystonia was investigated by study of four other cases of the syndrome, but they disclosed no abnormal iron pigment. The authors conclude that dystonia is a symptom complex which may be found in association with various pathologic changes.

Since Hallervorden-Spatz disease is a clinicopathologic entity, the authors do not classify the second case as an instance of this disease.

ALPERS, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

FAMILIAL DEGENERATION OF THE CEREBRAL GRAY MATTER IN CHILDHOOD. FRANK R. FORD, SAMUEL LIVINGSTON, and CHARLES V. PRYLES, J. Pediat. **37**:33 (July) 1951.

Precise classification of the different types of cerebral degeneration in childhood is impossible in the light of our present knowledge. In a general way, there are three main groups of disorders: the lipid cell degenerations, cerebral sclerosis, and degeneration affecting primarily the cerebral gray matter.

Ford and his associates report four cases of degeneration of the cerebral gray matter and review the pertinent literature. The clinical features include convulsions, myoclonus, spasticity, choreoathetosis, cerebellar ataxia, and dementia. The course is progressive, the outcome fatal. In infants the diagnosis is difficult. The onset is always before the end of the first year. Convulsions are usually seen. Myoclonus, hyperkinesia, choreoathetosis, and ataxia may or may not be present. Rigidity is probably present in all. However, the pattern may not be apparent, and one may see merely progressive deterioration, convulsions and rigidity.

In juvenile patients, between the ages of 3 and 6 years, there is usually a history of retarded development. As a rule, the onset of the progressive phase is marked by convulsions or petit mal (head-dropping). Convulsions are restricted to one side or the other and are closely associated with fine muscular twitchings. Hemiparesis may follow convulsions. Neither cerebellar ataxia nor choreoathetosis are prominent symptoms. As the condition progresses, mental deterioration and, perhaps, deafness and blindness may occur. The electroencephalogram, pneumoencephalogram, and the spinal fluid are not diagnostically useful.

At autopsy the brains of these children always show degeneration of the deeper layers of the cerebral cortex and sometimes degenerative changes in the basal ganglia of the forebrain, thalamus, and cerebellum.

The disease may be familial.

MACDONALD, Pittsburgh.

THE EFFECT OF ADRENOCORTICOTROPIC HORMONE IN EPILEPSY. ROBERT KLEIN and SAMUEL LIVINGSTON, J. Pediat. **37**:733 (Nov.) 1950.

Klein and Livingston obtained clinical improvement with parallel changes in the electroencephalogram in four epileptic children treated with corticotropin. Two other patients showed no definite improvement under such treatment, and in one of these corticotropin administration had to be stopped because of side-effects. Desoxycorticosterone acetate improved the electroencephalogram of one of two patients given the drug. The authors think that the beneficial effects of adrenal hormones may be due to their effect on carbohydrate, protein, and fat metabolism.

MACDONALD, Pittsburgh.

THE TREATMENT OF EPILEPSY BY CORTICAL EXCISION. A. EARL WALKER, J. Pediat. **38**:285 (March) 1951.

When medical treatment has failed, focal epilepsy may be relieved by surgery. Walker illustrates this point with three cases. Subpial resection, partial lobectomy, and hemispherectomy were accomplished. The three children were improved after operation.

MACDONALD, Pittsburgh.

THE REMISSION OF ATHETOTIC SHOULDER TREMORS THROUGH THE USE OF NON-MUSICAL SOUND STIMULI. LYDA M. SCHMELING, J. Speech & Hearing Disorders **16**:264-262 (Sept.) 1951.

A 28-year-old man with cerebral palsy and severe athetosis of both upper and lower extremities was subjected to a series of sound stimuli to increase the amount of athetosis of the shoulder-girdle. Cessation of the sound stimuli was followed by the remission of the athetosis.

PALMER, Wichita, Kan.

ENCEPHALITIS AND ENCEPHALOMYELITIS IN ENGLAND AND WALES DURING THE LAST DECADE. J. G. GREENFIELD, Brain **73**:141 (June) 1950.

Greenfield reports on a survey of virus encephalitis which occurred in England and Wales during 1939. Although encephalitis was rare during this period, the cases tended to fall into four groups with characteristic clinical syndromes and histological pictures. 1. The acute polioclastic type was of two days' to four weeks' duration. The onset was with headache, malaise, vomiting, and fever, going on to delirium, drowsiness, and unconsciousness. Epileptiform fits were common; paralysis of the cranial nerves and of the limbs was unusual. Examination of the cerebrospinal fluid revealed a moderate increase in cells, chiefly lymphocytes; elevation of the protein; high pressure, which decreased during the course of illness, and normal concentration of glucose and chlorides. Histologically, the inflammation was confined almost wholly to the gray matter; its intensity and location varied greatly. There was usually a meningeal exudate around the larger veins. 2. Acute hemorrhagic leucoencephalitis was characterized clinically by hemiplegia of fairly rapid onset. The cerebrospinal fluid showed a high cell count. The inflammation tended to affect the central parts of the centrum ovale and spread to the crus of the midbrain, the pons, and the cerebellar peduncles. Microscopically, there was an intense exudate of polymorphonuclear leucocytes, especially around the vessels. There were necrosis in the perivascular zones and fibrinous exudate into the vessel walls. The cortex was relatively unaffected. 3. Subacute inclusion-body encephalitis tended to occur in children aged from 4 to 16 years. The symptoms were progressive over a period of weeks, with loss of mentality and decerebrate rigidity later in the illness. Myoclonic jerkings or spasms were common. Death usually occurred seven weeks to six months after appearance of the first symptom. The cerebrospinal fluid characteristically showed a colloidal gold curve characteristic of dementia paralytica. The histological appearance was that of a polioclastic process, with secondary degeneration of the white matter. There were perivascular inflammatory changes and various stages of neuronal degeneration, progressing to complete loss of nerve cells. In many of the degeneratel neurons acidophilic

hyaline inclusion bodies were seen both in the nucleus and in the cytoplasm. At a later stage the cell might consist only of a rounded inclusion body. 4. Subacute sclerosing encephalitis occurred in children between the ages of 5 and 14 years. The onset was insidious, and involuntary movements were frequent. The cerebrospinal fluid showed only first- and second-zone colloidal gold curves. Histologically, the white and the gray matter were affected to equal degrees. There were diffuse mobilization of the microglia, infiltration of the plasma cells, and diffuse neuroglial sclerosis. Evidence of neuronal damage was comparatively slight.

FRANKEL, Philadelphia [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

THE GUILLAIN-BARRÉ SYNDROME, OR POLYRADICULONEURITIS. G. DEAN, South African M. J. **25**:293 (April 28) 1951.

Five cases of Guillain-Barré syndrome are reported, with a brief discussion of the history of the disease.

McGUIGAN, Evanston, Ill.

INSULIN THERAPY IN CHOREA MINOR. E. Mayerhofer, Ann. pædiat. **176**:297 (May) 1951.

In the first (acute) phase of chorea minor two to three injections daily of 3 to 7 units of insulin had a good and quick effect in improving muscular restlessness when sugar was offered orally at the same time and the rest of the diet contained an abundance of carbohydrates. The author thinks that his new treatment is based on two factors: first, on a central, perhaps hormonal, improvement of the muscle action and, second, on a nutritional improvement and an increase of the poor muscular tone (new formation of muscle glycogen and local depot formation).

FROM THE AUTHOR'S SUMMARY.

SUBACUTE SCLEROSING LEUCOENCEPHALITIS WITH INCLUSION BODIES. F. MARTIN, J. MACKEN, and R. HESS, Schweiz. Arch. Neurol. u. Psychiat. **66**:217-260, 1950.

Progressive dementia began to develop in a boy aged 7 years 3 months after the onset of whooping cough. Examination revealed aphasia, apraxia, right spastic hemiparesis, with tremors of the right upper extremity, and papilledema. Convulsive seizures and a rather constant elevation of temperature were observed. Eight weeks after the onset of cerebral symptoms, the patient became subject to generalized clonic movements, which were rhythmic in character, accompanied with transient loss of muscular tonus, and synchronous with bursts of theta waves in the electroencephalographic tracings. Electroencephalography also revealed epileptogenic foci, which were subsequently found to correspond to areas of cerebral necrosis. A state of decerebrate rigidity ultimately developed, and the child died of hyperpyrexia four months after the appearance of mental changes.

Anatomically, this case differed from one previously reported under the same title by van Bogaert (*J. Neurol., Neurosurg. & Psychiat.* **8**:101, 1945) by the existence of focal necrosis in both the cerebral cortex and the white matter and the presence of intramuscular and intracytoplasmic inclusion bodies. Focal necrosis and the relatively slight degree of demyelination were most evident in the occipital lobes. The glial and mensenchymovascular reaction was pronounced, especially about the necrotic areas and in the subcortical portions of the white matter. Collections of lymphocytes and plasma cells were observed in the cortex, as well as in the white matter. Degenerative changes involving the basal nuclei were most intense in the pallidum, the dentate nuclei, brain stem, and spinal cord being affected to a less degree. Observations following the inoculation of white mice with spinal fluid and a suspension of brain and spinal cord indicated that the lethal powers of the assumed virus increased with each passage.

DANIELS, Denver [A. M. A. ARCH. NEUROL. & PSYCHIAT.].

CONTRIBUTION TO THE PSYCHOPATHOLOGY OF HYDROCEPHALUS CONGENITUS INTERNUS AND LATE CONSEQUENCES OF EPIDEMIC MENINGITIS. A. GLAUS, Schweiz. med. Wchnschr. **22**:523 (June 2) 1951.

Two cases of congenital internal hydrocephalus are reported. In one case disorders of character with states of excitability were evaluated as a cerebral local psychosyndrome. In the other

this psychosyndrome also manifested itself in an abnormal development of character. The paper stresses the *hirnlokales Psychosyndrome* of Bleuler. The histories of these cases are given in detail.

AMBERG, Rochester, Minn.

THE ELECTROENCEPHALOGRAM AND RECENT THERAPEUTIC METHODS FOR PETIT MAL EPILEPSY. C. LOMBROSO, Minerva pediat. **2**:393 (Sept.) 1950.

Eleven cases are reported, illustrating the clinical and electroencephalographic characteristics of petit mal epilepsy and the therapeutic value of the drug trimethadione (tridione®) in this condition.

HIGGINS, Boston.

SUBDURAL FLUID AND ACUTE PURULENT MENINGITIS. JULIO MENEGHELLO and CARMEN AGUILO, Rev. chilena pediat. **22**:91 (March) 1951.

Meneghello and Aguilo present 7 cases of purulent meningitis during the course of which a subdural collection of fluid was found. The authors believe the subdural fluid is secondary to the meningitis. They stress the importance of this occurrence, which seems to be frequent and which explains the maintenance or appearance of some symptoms after the meningeal infection is cured. Differential diagnosis is presented in 4 cases in which the subdural accumulation of fluid was probably previous to the purulent meningitis.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF PURULENT FORMS OF MENINGITIS IN CHILDHOOD ACCORDING TO PRINCIPLES IN FORCE AT PRESENT. HELMUT WALENZ, Med. Klin. **44**:1397 (Nov. 4) 1949.

A total of 52 children with purulent meningitis were treated over a period of four years. The bacteria involved were Meningococci, Pneumococci, Staphylococci, Streptococci, Bacteria influenzae and Salmonella.

Meningococcus meningitis was treated with sulfonamides. For patients with Waterhouse-Friderichsen syndrome, or those in whom the fever did not yield promptly, a combination of sulfonamide with penicillin was used. Of 23 patients, 7 died, including those admitted in a moribund state. Of the 19 patients with pneumococcic meningitis, 13 were below 1 year of age. Of the 19, 9 came in moribund and died; of the others, 2 could be saved with combined sulfonamide and penicillin therapy. All five patients with influenzal meningitis died in spite of sulfonamide, penicillin, and streptomycin therapy. Three of these patients were less than 1 year old; the others were 12 and 14 months. For Salmonella infections a combination of sulfonamide and streptomycin is recommended. Of four patients with meningitis due to Staphylococci two were cured by sulfonamides alone, the other two by sulfonamides and penicillin, a combination recommended for Streptococcus meningitis also.

AMBERG, Rochester, Minn.

SIGNIFICANCE OF CHVOSTEK'S SYMPTOM IN INFANTS UNDER TWO YEARS. KJELL L. MÖLLER and BERTIL SÖDERLING, Acta pædiat. **37**:318, 1949.

The positive facial phenomenon of Chvostek's symptom frequently can be found in infants and children under 2 years of age without coexistent symptoms suggestive of infantile tetany. The phenomenon may be elicited in unchanged form for many years. It thus appears that its presence in the spasmophilic age may be of the same innocent nature as it is in older children. Neither does it seem to be pathognomonic of neuropathy.

FROM THE AUTHORS' SUMMARY.

CONGENITAL HYDROCEPHALUS IN A NEWBORN INFANT: EPIDEMIC HEPATITIS IN THE MOTHER IN THE SECOND AND THIRD MONTHS OF PREGNANCY. ARNE KASS, Acta pædiat. **40**:239 (May) 1951.

A case is reported of a boy admitted to the University Pediatric Hospital in Bergen when only one day old. There was marked hydrocephalus and microphthalmos at birth, but no other deformities were found. There was no evidence of syphilis or toxoplasmosis. The patient died when 8 weeks old.

A postmortem examination showed a severe hydrocephalus externus (1,760 ml. of fluid) and a brain compressed into a small lump at the base of the skull. The shape and size of the cerebellum, pons, and medulla oblongata were normal, whereas the cerebrum was represented by a mass of white brain matter of the size of a walnut. It is possible that the hydrocephalus was originally an internal hydrocephalus, for what was left of the cerebrum presented itself as a sac showing signs of having been ruptured.

The patient's mother had suffered from epidemic hepatitis in the second and third months of her pregnancy, during which she had otherwise been perfectly fit, exposed to neither injury nor x-rays. The abnormal conditions in the child, corresponding as they do to the conditions often found in children whose mothers have suffered from some virus disease during pregnancy, are taken to be the outcome of the acute infectious hepatitis from which the mother suffered during the fetal organogenetic period.

FROM THE AUTHOR'S SUMMARY.

Psychology and Psychiatry

DEVELOPMENT OF SOCIAL SKILLS AS AN INSTRUMENT IN SPEECH THERAPY. JANE BEASLEY, J. Speech and Hearing Disorders **16**:241-245 (Sept.) 1951.

Speech lessons may be profitably directed around social skills, serving three useful purposes: (1) a way of working on the mechanics of speech production; (2) the development of such skills within a real situation; (3) production of feelings of confidence and independence and similar evaluations on the part of the speech-corrected child.

M. F. PALMER, Wichita, Kan.

EMOTIONAL PROBLEMS OF THE INVALID CHILD. RAMON DE LA FUENTE M. and LEONOR TORRES, Bol. méd. d. Hosp. inf., México **7**:194 (April) 1950.

The authors point out the repercussions that certain forms of invalidism may have in the development and functioning of the personality of children.

Several of the mechanisms, such as the hostility of the environment, the aggressiveness of healthy children, the conscious or subconscious repulsion on the part of the parents, the sense of inferiority, etc., are analyzed. The commoner ways in which disabled children react are also pointed out: the regressive attitude that turns a child into an emotional invalid; the conscious or subconscious utilization of the invalidism as defense; the hypercompensation reaction shown in aggressive and cruel conduct.

The authors also note the role that invalidism may have in certain sexual deviations. Several clinical cases are presented to illustrate the theoretic consideration.

Finally, the fundamental rules for the handling of the disabled child are pointed out, as well as the therapeutic resources of a psychologic order which must be put into practice.

FROM THE AUTHORS' SUMMARY.

DYNAMIC ASPECTS OF HISTORY TAKING IN PEDIATRICS. CARLOS A. BAUZA, Arch. pediat. Uruguay **12**:587 (Aug.) 1951.

History taking offers great possibilities for mental hygiene, if only the pediatrician allows himself to "listen." Generally speaking, the questioning of parents is impersonal, and often it shows negative feelings, such as hostility or criticism.

These negative feelings, even though subtle, are realized and destroy the dynamic aspects of history taking, as well as the possibilities of constructive psychological interaction around the situation.

Avoiding identification with the child or with the parents, accepting parent hostility and anxiety without reacting with the same feelings, frequently causes the so-called "chief complaint" to recede, displaced by problems which threaten the parents' emotional integrity much more.

The pediatrican should develop knowledge and skill in interpersonal relationships through practical experience and qualified supervision.

FROM THE AUTHOR'S SUMMARY.

Diseases of Genitourinary Tract

OUTBREAK OF ACUTE NEPHRITIS IN ADOLESCENT SCHOOLBOYS. C. HENRY KEMPE, RICHARD W. OLMSTEAD, and EDWARD C. CURNEN, Pediatrics **8**:393 (Sept.) 1951.

An outbreak of acute nephritis is reported which occurred among adolescent boys who were students at a private day school. Four boys in one class had clinically typical acute glomerular nephritis. Seventeen other members of this and one other class were found to have hematuria with or without associated albuminuria. The total incidence of hematuria among the 73 students in these two classes was 29%. Of the 21 boys with hematuria, 15 still had abnormally elevated Addis sediment counts approximately seven weeks after the initial examination.

Cultures of the nasopharynx were made from 85 students. Hemolytic streptococci were detected in 11 (13%) of the boys, including 3 with hematuria. The results of attempts to identify the streptococci by serologic technics indicated that at least five immunologically different varieties were represented.

Determinations of antihyaluronidase, antistreptolysin "O," and antistreptokinase in serum from 17 boys with hematuria and 20 without apparent hematuria revealed wide variations in titer but no significant difference between the two groups. FROM THE AUTHORS' SUMMARY.

ACTH IN LIPOID NEPHROSIS. C. HOOFT and R. CLARA, Maandschr. kindergeneesk. **19**:346 (Oct.) 1951.

The clinical course and especially the changes in the total protein, the albumin, and the alpha, beta, and gamma globulin were studied in two children with lipoid nephrosis, during and after a treatment with corticotropin (ACTH).

The results were compared with data obtained from two other patients with lipoid nephrosis, in whom a spontaneous remission was observed. The clinical course was nearly the same. In the patients treated with corticotropin the serological symptoms of a lipoid nephrosis remained practically unchanged. In the cases of spontaneous remission, however, the hypoproteinemia disappeared, the different protein fractions became normal, and normal cholesterol, total lipoid, and calcium levels were obtained. FROM THE AUTHORS' SUMMARY.

Diseases of Ductless Glands; Endocrinology

SYNDROME OF OVARIAN AGENESIS (CONGENITALLY APLASTIC OVARIES): SHORT STATURE, MULTIPLE CONGENITAL ABNORMALITIES AND HIGH URINARY GONADOTROPINS IN A TWO YEAR, EIGHT MONTH OLD FEMALE. HENRY K. SILVER, Pediatrics **8**:368 (Sept.) 1951.

A proved case of the syndrome of ovarian agenesis, short stature, multiple congenital abnormalities, and high urinary gonadotropins in a girl of 2 years 8 months, is presented. Congenital anomalies included webbed neck, abnormalities of the feet, a moderate degree of cubitus valgus, and defects of the vertebrae. Only slight retardation of epiphyseal development was present by the fourth year of life. Because of the marked variations in the levels of urinary gonadotropins in this patient, it is suggested that more than one assay should be performed in a preadolescent girl before it is concluded that the gonadotropins are not increased.

FROM THE AUTHOR'S SUMMARY.

SUPRARENAL SYMPATHICOBLASTOMA WITH BONE METASTASES. G. RUBINO, Lattante **22**:423 (July) 1951.

A child of 3½ years had a malignant abdominal tumor with metastases to the skull, and bilateral protrusion of the eyeballs. Autopsy revealed that the tumor originated in the adrenal gland and was histologically a sympathicoblastoma.

HIGGINS, Boston.

THE MONOSYMPTOMATIC FEBRILE FORMS OF HYPERTROPHY OF THE THYMUS. FRANCISCO DUCASSI Y LOPEZ-DORIGA, Arch. med. inf. **20**:165 (July-Aug.-Sept.) 1951.

Of a total of 43 children studied, only 31 fall into the pure monosymptomatic febrile form. The author believes the following conclusions to be justified:

1. Notwithstanding the reluctance of the majority of pediatric schools, especially the American, to accept the thymic pathology, this noxa is a condition which, in Cuba, is becoming more frequent every day.

2. The monosymptomatic febrile form is an important variety which seldom occurs, and which often remains undiagnosed.

3. This clinical form occurs most frequently during the first few days or weeks of the patient's life, and it has a marked predilection for white males.

4. High temperatures appear more often among the newborn, and febricula among the children several months old. This last variety is the one most frequently encountered in daily practice.

5. Although at present the products of thymic secretion cannot be identified with certainty, proof of their existence has been established.

6. It may be that the fever is produced by a humoral mechanism. Hormone?

7. Palpation of the superior pole of the thymus, and percussion of its borders are methods of little value in the diagnosis of this affection.

8. Frequently found in the hemogram of all these febrile forms is a high and constant lymphocytosis with a variable eosinophilia.

9. Simple x-ray pictures are always a useful means of diagnosis, especially in the typical or classical forms.

10. Artificial anterior pneumomediastinum is the method par excellence. It makes possible a clear and precise diagnosis, especially in atypical forms of hypertrophy of the thymus. In addition, it is simple, practical, and harmless.

11. Fluoroscopic examination should always be made when this condition is suspected.

12. The diagnosis of febrile monosymptomatic forms should be determined by elimination, after the thymic hypertrophy has been demonstrated by x-ray examination, after the hematologic changes have been established, and lastly after disappearance of the fever under proper radiotherapy.

13. Differential diagnosis should be established, with respect to all those processes capable of producing fever in children, especially as to fever due to thirst or dehydration in the newborn, and that caused by lesions or defects of the thermoregulatory nervous centers; also with respect to infections of the Waldeyer lymphatic tissues, catarrhal virus infections, and, very particularly, primary tuberculous infections.

14. The thymus is very resistant to radiotherapy in its normal state, but when it is in a pathologic or hyperfunctional condition the contrary is true.

15. The author has not observed any ill effects among the children treated with radiotherapy. He believes that, employed in appropriate doses, with correct techniques, this therapeutic measure cannot produce any ill effects.

16. The duration of the condition in all his cases was short, and only in three of them was it necessary to repeat the radiotherapeutic doses to effect complete recovery.

17. The favorable prognosis in these forms is due to the greater knowledge of the disease, as well as to the means which can be counted on today for its correct diagnosis.

FROM THE AUTHOR'S SUMMARY.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

OSTEOID OSTEOMA. MALCOLM B. DOCKERTY, RALPH K. GHORMLEY, and ALFRED E. JACKSON, Ann. Surg. **133**:77-89 (Jan.) 1951.

In 1935 Jaffe described, under the title "osteoid osteoma," a peculiar lesion of bone. Clinically the lesions behaved like atypical osteomyelitis, and roentgenologically they exhibited many of

the features of the sclerosing osteomyelitis of Garré. Microscopically the lesions lacked the features of inflammation and presented instead many of the elements of a benign neoplastic condition.

The authors summarize the clinical and pathologic features in 20 cases in which diagnosis was confirmed by microscopic examination.

Surgical excision is the treatment of choice. Whether spontaneous healing or regression of this lesion may occur seems to the authors to be a problem which cannot be solved in the light of present knowledge.

BANTIN, Omaha.

CONGENITAL STIPPLED EPIPHYSES. G. DAVID FORD, MARTIN SCHNEIDER, and JAMES R. BRANDON, Pediatrics **8**:380 (Sept.) 1951.

Two infants, one full-term, the other premature, presenting findings of "congenital stippled epiphyses" (chondrodystrophia calcificans congenita, dysplasia epiphysialis punctata) are described. The characteristic feature of the entity is the presence of multiple, discrete, dense, calcific stippling in many cartilaginous epiphyses and apophyses. The diagnosis necessarily rests on roentgenographic examinations. The full-term infant exhibited shortening of the proximal long bones of the extremities and bilateral congenital cataracts. Autopsy studies were made on the premature infant. Histologic features were similar to those previously described, namely, an irregular pattern of bone formation, with areas suggesting mucoid degeneration, which were most prominent in the vertebral bodies.

FROM THE AUTHORS' SUMMARY.

A CASE OF MYOSITIS IN A GIRL OF FIVE YEARS—DIAGNOSTIC CONSIDERATIONS. C. SAINZ DE LOS TARREROS AMEZAGA, Acta pediat. españ. **9**:173 (Feb.) 1951.

The patient was a 5-year-old girl who had been well up to the onset of the present illness and had no history of familial diseases.

The muscles had a hypertonicity which could almost be said to be tumor-like. The symptom appeared first in the neck and face but progressed slowly to the trunk muscles and those of the extremities until movement and walking were difficult. The child had some fever and the disease had been diagnosed as "rheumatic fever," but there was no pain.

There were 21% eosinophiles, but muscle biopsies showed no parasites. Diagnostic possibilities considered were : (1) lesion in central nervous system; (2) specific myositis of the various types; (3) trichinosis; (4) drug intoxication.

The first was ruled out because on examination the findings did not correspond to those due to lesion in the pyramidal or extrapyramidal tract, nor to meningeal or cerebellar lesions. Neither did the appearance of the child suggest hysteria. Drugs such as ergot, strychnine, etc., were ruled out by the history and the fact that tetanic manifestations were not present.

Although the child had eosinophilia, there was no history of the ingestion of pork; no other cases of trichinosis had been reported in the village; there were no muscle pains and no palpebral edema such as is usually seen. There had been no history of diarrhea and colic, which are the first signs of a parasitic invasion. Tests with Trichinella antigen (which are not actually pathognomonic) gave negative results. The child did not respond to arsenicals, which were used frankly as symptomatic medication.

The lack of clinical evidence for trichinosis leads the author to believe this to be a specific myositis. He then classifies the types of myositis, and diagnoses this case as myositis ossificans progressiva (Münchmeyer's disease), but with some feeling still that it may be an atypical case of trichinosis. The slow onset, the appearance in early childhood, the tumor-like action of the muscle, slight fever, and little pain, all point to progressive myositis ossificans.

Treatment is of course very limited—massage, diathermy, radium therapy, and symptomatic analgesics.

ALLEN, Santa Fe, N. M.

Diseases of Eye

RETROLENTAL FIBROPLASIA: A STATISTICAL STUDY WITH PARTICULAR REFERENCE TO THE EFFECT OF VITAMIN A. JOSEPH DANCIS, J. M. LEWIS, and LOREN P. GUY, New England J. Med. **245**:402 (Sept. 13) 1951.

The incidence of retrolental fibroplasia in the premature unit at Bellevue Hospital for the period of November, 1946, to October, 1950, is reported.

Between November, 1946, and March, 1948, a water-miscible vitamin D preparation was used routinely. During this period the incidence of retrolental fibroplasia was extremely low.

Beginning in March, 1948, a water-miscible multivitamin preparation containing vitamin A was substituted for the vitamin D. The incidence of retrolental fibroplasia remained unchanged until May, 1949. This persistently low incidence for over a year makes it very unlikely that the vitamin A preparation is a factor in the production of retrolental fibroplasia.

Since May, 1949, the incidence of retrolental fibroplasia has been rising. As the incidence has risen, the infants with high birth weights have become involved. The rise in incidence occurred despite the fact that practices concerning transfusions, supplementary iron, exposure to light, and the initial starvation period remained unchanged.

FROM THE AUTHORS' SUMMARY.

SYMPTOMATIC TREATMENT OF VERNAL CONJUNCTIVITIS WITH ANTISTINE. I. BRAND, Schweiz. med. Wchnschr. **81**:923 (Sept. 22) 1951.

Eye drops with 5% antazoline (antistine®) hydrochloride and 0.25% naphazoline (privine®) hydrochloride were administered three times a day to 10 children, 2 to 14 years old. In addition, 0.1 gm. of antazoline hydrochloride was administered by mouth two or three times a day. The vernal conjunctivitis was pronounced and the diagnosis certain. The response was very satisfactory.

AMBERG, Rochester, Minn.

CASE OF TRACHOMATOUS KERATITIS. ALFREDO DABANCENS L. and WALDO INOSTROZA C., Rev. chilena pediat. **22**:294 (July) 1951.

A case of trachoma in a girl 13 years and 9 months old is described. Both her mother and an older sister had the same disease. In the patient a vascularized pannus and scars in the superior tarsal conjunctivae of both eyes were the predominant symptoms. The disease had been present for nine years. Local sulfanilamide and penicillin treatment and intramuscular penicillin injections were producing good results after one month's trial.

FROM THE AUTHORS' SUMMARY.

MARCUS GUNN'S PHENOMENON IN INFANTS. H. PAU, Kinderärztl. Praxis **17**:100 (March-April) 1949.

A 10-month-old infant showed synchronous raising of the eyelid with opening of the mouth. About 100 cases of synchronous movements of lid and mouth are reported in the literature, most of them showing symptoms of association of the nuclei of the oculomotorius (levator palpebri) and trigeminus (musculus pterygoideus) nerves, such as raising the eyelid at the time of moving the jaw in the opposite direction.

GLASER, Jerusalem, Israel.

Cutaneous Diseases; Allergy

SCLERODERMA HEART DISEASE. J. HURLY, J. COE, and L. WEBER, Am. Heart J. **42**:758 (Nov.) 1951.

The authors report the case of a man who showed symptoms of scleroderma at the age of 51. After several exacerbations and remissions of symptoms, he died of congestive heart failure two years after the onset of scleroderma. Sections of the myocardium revealed in all parts of

the heart a marked overgrowth of connective tissue. There was also destruction of the muscle parenchyma in varying degrees.

Although scleroderma heart disease is a rare cause of heart failure, the possibility of this eventuality must be kept in mind in cases of scleroderma.

GIBSON, Chicago.

A STATISTICAL STUDY OF THE EMOTIONAL COMPONENT IN ALLERGY: ITS RELATIONSHIP TO THE AGE AND SEX DISTRIBUTION OF 5,583 PATIENTS. MILTON B. COHEN and LEWIS E. ABRAM, J. Allergy **20**:207 (May) 1949.

These observations confirm those of other studies that allergic conditions occur more frequently in males than in females from birth to 15 years and more frequently in females than in males from the ages of 15 to 45. It is possible that an unknown factor associated with puberty may be responsible for this difference in distribution. Emotional disturbances which initiate attacks occur more frequently in women than in men between the ages of 20 and 40.

HOYER, Cincinnati.

THE EFFECT OF CORTISONE ON BRONCHIAL ASTHMA AND HAY FEVER OCCURRING IN SUBJECTS SENSITIVE TO RAGWEED POLLEN. HADDON M. CARRYER, GILES A. KOELSCHE, LOUIS E. PRICKMAN, CHARLES K. MAYTUM, CLIFFORD F. LAKE, and HENRY L. WILLIAMS, J. Allergy **21**:282 (July) 1950.

Cortisone was given to three patients sensitive to ragweed pollen who had bronchial asthma during the hay fever season. Suspensions of 100 mg. of cortisone or cholesterol were given intragluteally daily for a period of weeks. The patients and the physicians were not aware of which drug was being given or when it was given until after the conclusion of the period. A comparison of the symptoms following the injection of each of the drugs was made at the end of the season.

The patients had immediate relief from asthmatic symptoms following the injection of cortisone; the effect was as great on other manifestations of hay fever. The relief of symptoms was confined to the period during and immediately following the injection of cortisone.

HOYER, Cincinnati.

ACTH AND CORTISONE IN ALLERGIC MANIFESTATIONS: THERAPEUTIC RESULTS AND STUDIES ON IMMUNOLOGICAL AND TISSUE REACTIVITY. SAMUEL M. FEINBERG, THURMAN B. DANNENBERG, and SAUL MALKIEL, J. Allergy **22**:195 (May) 1951.

A study was made of 15 patients with asthma, 4 patients with allergic dermatoses, and 3 with hay fever. The therapeutic effect of the hormones was observed under "objective and controlled conditions."

The authors believe that the hormones have value in the temporary treatment of certain types and phases of allergic syndromes. They are useful in intractable asthma, in acute status asthmaticus, and in severe drug reactions. There are limitations in the usefulness of the hormones. They are not substitutes for basic allergic management. There are dangers and hazards in the use of these hormones. It is possible for a person to be sensitive to them.

The skin reaction to antigens and histamine were unchanged in patients treated with corticotropin (ACTH) or cortisone.

Ophthalmic and nasal reactions were not significantly altered. Sensitizing antibodies remained unaffected after therapy with corticotropin or cortisone. The authors deplore the abuses in the use of the hormones in allergic patients who would respond to sound allergic treatment.

HOYER, Cincinnati.

ACTH AND CORTISONE IN ALLERGIC DISEASES: CLINICAL, SEROLOGIC (ELECTROPHORETIC), AND IMMUNOLOGIC STUDIES. ROBERT A. COOKE, WILLIAM B. SHERMAN, ARTHUR E. O. MENZEL, H. BEECHER CHAPIN, CHARLES M. HOWELL, ROLAND B. SCOTT, PHYLLIS A. MYERS, and LILLIAN M. DOWNING, J. Allergy **22**:211 (May) 1951.

Studies were conducted on children and adults with asthma, caused chiefly by an infection, with dermatitis, or with urticaria. The authors believe that the hormones, corticotropin (ACTH) and cortisone, are the best means for attaining symptomatic relief but that they do not influence the course of the disease. They afford physical rest and improve nutrition and hydration in chronically ill patients. The efficacy of these drugs should not deter one from the study for the cause of the symptoms. A diagnosis of the cause is important for long-term effective management of the condition. The authors caution against indiscriminate use of the hormones, since they mask symptoms and do not cure disease. By lowering the temperature and the leucocyte count they may prevent diagnosis of a more serious condition, such as bacteremia or peritonitis.

HOYER, Cincinnati.

ALLERGIC REACTION TO AUREOMYCIN WITH A DEMONSTRATION OF A POSITIVE SKIN TEST TO SERUM CONTAINING AUREOMYCIN. EARL B. BROWN and MAURICE GOODGOLD, J. Allergy **22**:273 (May) 1951.

An angioneurotic edema and rash developed in a patient following the ingestion of aureomycin. The patient also had an exacerbation of eczema solare. A year previously she had a rash and angioneurotic edema, with an exacerbation of eczema solare, following the use of penicillin.

Aureomycin serum, which is now available, gave an immediate skin reaction; a delayed positive reaction of the skin was produced by aureomycin solution.

HOYER, Cincinnati.

WOOL AS A CAUSE OF ECZEMA IN CHILDREN. LEWIS WEBB HILL, New England J. Med. **245**:407 (Sept. 13) 1951.

Recurrence or intensification of childhood eczema is often noted with the onset of winter. Although house dust is often to blame, Hill points out that wool sensitivity from the ubiquitous wool of cold weather garments may frequently be the provocative factor. In 40 children between 2 and 12 years, 14 patch tests for wool were positive. The technique of this test and certain details concerning the site of sensitization in the skin layers are presented.

Treatment of this disorder involves as much avoidance of wool as is possible and protection of the skin by suitable salves covered over with an elastic bandage and by white cotton gloves for the hands.

Although hyposensitization procedures are rarely used when directed toward wool allergy, the author noted good results when they were carried out in three patients. Lower doses are given than in respiratory allergy from the same environmental allergen for fear of aggravation of symptoms.

WHEELOCK, Denver.

THERMAL ALLERGY. HERBERT J. RINKEL, South. M. J. **44**:1067 (Nov.) 1951.

An interesting concept of the cause and management of some types of allergic disease of the respiratory tract is presented. It is based on 14 years of observation. The synergistic etiologic role of foods or inhalants and contact with thermal changes, chiefly cold, is emphasized. Recognition of this role aids in the treatment of patients having allergic disease on such a basis.

LOGAN, Rochester, Minn.

INFANTILE ECZEMA. S. GORDON, South African M. J. **25**:697 (Sept. 22) 1951.

Eczema is discussed thoroughly from an etiologic standpoint. Similarity between atopic eczema and dermatitis herpetiformis is pointed out, and the author states that treatment with

paraaminobenzoic acid, or sulfapyridine has been extremely useful in the treatment of both diseases. He considers that the effect of these drugs on the epidermis is comparable to that of antihistaminic drugs on the dermis.

McGUIGAN, Evanston, Ill.

ICHTHYOSIS SIMPLEX. JORGE ROSSELOT and RODOLFO BURDACH, Rev. chilena pediat. **22**:374 (Sept.) 1951.

The clinical characteristics and histopathological findings in the cases of six patients with ichthyosis simplex are described. In four cases there was a familial congenital history. The most important clinical symptoms were roughness of the skin and laminar desquamation, hyperpigmentation and follicular hyperpigmentation, and follicular hyperkeratosis. In four patients during the summer months a partial and transitory remission was noted. The follicular hyperkeratosis and the Malpighian atrophy were the most constant histological findings, while infiltration and edema of the dermis, basal hyperpigmentation, and absence of the granulosa layer were less commonly found.

FROM THE AUTHORS' SUMMARY.

ERYTHEMA NODOSUM. GUNTHER MARTENS, Deutsche med. Wchnschr. **75**:356 (March 17) 1950.

Erythema nodosum in childhood demands the search for a primary tuberculosis.

AMBERG, Rochester, Minn.

INCONTINENTIA PIGMENTI (BLOCH-SULZBERGER). W. KÜNZER and H. ZEISEL, Ztschr. Kinderh. **66**:411, 1949.

In a 5-month-old infant symptoms consisted of maculopapular brown pigmented spots in linear arrangement on trunk and extremities. Histologic examination showed a melanin deposit in the cells of the cutis. Only 13 cases have been described in the literature. The fact that 11 were in children leads to the conclusion that the lesions must disappear before the children reach adulthood.

GLASER, Jerusalem, Israel.

ERYTHEMA NODOSUM RECIDIVANS. ROBERT NEUMANN, Pediat. listy **4**:196, 1949.

The theory of the pathogenic mechanism of the onset of erythema nodosum is not yet quite fixed and is now of great interest. In Scandinavia, it is of tuberculous origin in 95% of the cases and appears earliest at the age of 1½ years. The primary type is usually accompanied with a recent lung lesion; the postprimary type appears after the primary stage of tuberculosis has been overcome, after the sensitivity to tuberculin again changes from negative to positive. Erythema nodosum recidivans appears in some families and in disposed persons. It is brought about by some provoking factor; febrile illnesses, particularly infectious diseases, have been overcome. These persons have a primary tuberculous illness.

A case of erythema nodosum recidivans in a tuberculous child is reported. In the course of a primary erythema nodosum, a lung lesion was detected. Later on, after measles had been overcome, and after two intravenous doses of sulfathiazole had been given, erythema nodosum reappeared.

FROM THE AUTHOR'S SUMMARY.

PLASMA PROTEIN CHANGES IN ERYTHRODERMA AND SEBORRHEIC DERMATITIS AND THEIR RELATION TO BIOTIN DEFICIENCY. A. F. PALACKY and R. STRYCEK, Pediat. listy **5**:270, 1950.

In 16 infants suffering from desquamative erythroderma (Leiner-Houssous disease) and one with seborrheic dermatitis, hydroproteinemia was found. The deficiency mainly concerned the globulin fraction, and this was sometimes so low that the albumin-globulin ratio rose to even more than 5. The favorable response to treatment with biotin and meat hydrolysates, or with a combination of the two, seems to be a further proof of the deficiency being the etiological factor in these conditions. The authors advance the view that there is a close link between the biotin and the plasma proteins.

FROM THE AUTHORS' SUMMARY.

HERPES ZOSTER OF THE OPHTHALMIC REGION IN THE CHILD. ÅKE BJÖRK, Acta pædiat. **37**:363, 1949.

To get an idea of the incidence of zoster ophthalmicus in children, the author studied the hospital records of 291 cases of zoster ophthalmicus. The distribution in the different age groups is graphically presented. The curve thus constructed shows, first, that zoster ophthalmicus is commonest among old people; second, that it is very rare in children. Among the 291 cases, there were only two patients under 10 years of age. These two cases, in which the author personally followed up the evolution of the disease, are reported at greater length.

The characteristic clinical symptoms produced by zoster, in particular those marking the type localized to the face, are described. In view of the fact that zoster in children differs in several respects from that observed in adults, the author takes up the question of whether this applies also to zoster ophthalmicus in children.

FROM THE AUTHOR'S SUMMARY.

ACRODYNIA TREATED WITH "BELLERGAL." GÖSTA ÖBERG, Nord. med. **41**:71 (Jan. 14) 1949.

Typical acrodynia in a 1½-year-old girl was successfully treated with "bellergal" (a proprietary composed of belladonna alkaloids, ergotamine tartrate, and phenobarbital). The patient was discharged after 2½ months.

WALLGREN, Stockholm, Sweden.

ICHTHYOSIS AND EXSUDATIVE DIATHESIS. O. A. DRIESSEN, Maandschr. kindergeneesk. **19**:282 (Oct.) 1951.

A case of ichthyosis in a newborn infant is reported. Three other children of this family had the same skin disease at birth. These three chidren were also idiots. All these infants suffered from a recurring asthmatic bronchitis. The father, when a baby, had had a severe form of infantile eczema.

FROM THE AUTHOR'S SUMMARY.

ACUTE HEMORRHAGIC EDEMA, H. L. J. M. BARTELS, Maandschr. kindergeneesk. **19**:467 (Dec.) 1951.

The author describes the cases of three patients, respectively 23, 28, and 12 months old, in whom severe edema developed, localized mainly symmetrically and distributed over a large part of the skin. The edema soon became hemorrhagic. The process was considered to be of infectious origin in all three cases. Complete cure followed treatment with antibiotics, elimination deit, and calcium. The course of allergic reaction in such cases of acute hemorrhage edema is discussed. Emphasis is laid upon the antigen-antibody reaction in the tissues.

FROM THE AUTHOR'S SUMMARY.

Surgery and Orthopedics

CHANGE AND PROGRESS IN ANAESTHESIA. GEOFFREY ORGANE, Proc. Roy. Soc. Med. **43**:181 (March) 1950.

The rapid advances in the science of anesthesia are described. Technics and anesthetic machines have become more complicated, requiring a protracted period of training under supervision. Anesthetists must now be experts in intravenous, intrasternal, spinal, epidural, and local anesthesia. They must be laryngologists, tracheologists, and bronchologists. In addition, they must be guardian angels for some of the more radical surgeons. The anesthetist is legally responsible for the preoperative assessment of the patient's fitness for operation, for the selection of appropriate premedication, for the choice of anesthetic and technic, and for the care of the patient's health during the operation and until recovery from the anesthetic is complete. When possible, preoperative consultation with surgeon and internist is advisable. The anesthetist should be qualified to act as a resuscitation officer and be fully informed of all the theoretical and practical aspects of this work. Meticulously careful and accurate anesthetic records should be preserved.

HEARD, Monterey, Calif.

PLASTIC REPAIR OF CONGENITAL AND ACQUIRED DEFECTS OF THE FACE IN CHILDREN. H. PESKOVA, Pediat. listy **5**:267 (No. 6) 1951.

In defects of the face in children the surgeon's task is difficult and complicated. It is necessary to use various operative methods, and the treatment is often long and drawn out. The operations used in the individual defects are described briefly, and the time at which each operation is best undertaken is given. Illustrations show the type of defects and in some cases the condition before and after operation.

FROM THE AUTHOR'S SUMMARY.

Teeth and Dentistry

FLUORINE, DENTAL CARIES, AND THE THYROID. V. DEMOLE, T. VON FELLENBERG, A. J. HELD, and H. SCHMID, Bull. schweiz. Akad. med. Wissensch. **7**:440 (Oct.) 1951.

Clinical and chemical observations made on several groups of children of the same ethnologic origin in different parts of Wallis, Switzerland, show that there is a real relationship between the content of fluorine in the earth, water, and plants and the degree of fluorization of the hard dental tissues and their resistance to caries.

In the area of Sembrancher, where the drinking water contains 1.4 mg. of fluorine per liter, the resistance to dental caries is much higher than in children living in the vicinity of Le Chable, where the fluorine content of water is only 0.05 mg. per liter.

The concentration of 1.4 mg. of fluorine in water does not seem to have any toxic action on persons who have drunk this water from birth up to 15 years of age.

Fluorine at a concentration of 1.4 mg. per liter does not influence in any way the development of the thyroid gland.

FROM THE AUTHORS' SUMMARY.

Miscellaneous

PRENASAL AND PREORAL AUSCULTATION. JAMES L. WILSON, J. Pediat. **37**:759-761 (Nov.) 1950.

The physician may obtain invaluable information about a child's respiration by listening with the stethoscope held ½ to 1 inch (1.3 to 2.5 cm.) from the nose and mouth of the patient. This should be done before the patient is touched and before he is disturbed by removal of his clothing. In this manner one can accurately determine hyperpnea; the sum of tidal air and pulmonary ventilation can be evaluated. Pulmonary obstruction, irregularities of breathing, nasal obstruction and, with little practice, even rales may be distinguished.

MACDONALD, Pittsburgh.

FURTHER OBSERVATIONS ON THE EFFECT OF PROLONGED THIOPENTAL (PENTOTHAL) ANESTHESIA ON METABOLISM OF CARBOHYDRATES AND OF PROTEINS IN DOGS. WALTER M. BOOKER, DAVID M. FRENCH, and PEDRO A. MOLANO, J. Pharmacol. & Exper. Therap. **96**:145 (June) 1949.

Thiopental (pentothal®) sodium is said to be one of the most widely used anesthetic agents. In a previous work the authors had shown that prolonged thiopental sodium anesthesia caused a prominent and long-maintained increase in the blood sugar and reduction of the liver glycogen. In the present paper it is reported that insulin controls the blood sugar level, the blood lactate level, and prevents an extensive depletion of liver glycogen.

Their evidence seems to support the view that protein "protects" the liver better than carbohydrate, since animals on high protein diet showed higher quantities of glycogen in the liver and disposed of sulfobromophthalein sodium more efficiently than animals on high carbohydrate or on normal diets.

PILCHER, Cleveland.

THE INFLUENCE OF THE DOSAGE REGIMEN ON THE THERAPEUTIC ACTIVITY OF PENICILLIN G. L. H. SCHMIDT, ALICE WALLEY, and RICHARD D. LARSON, J. Pharmacol. & Exper. Therap. **96**:258 (July) 1949.

The results of this study should help clarify the much-discussed clinical administration of penicillin G. The experiments were made on a definite strain of 7- to 9-week old rats; the

McGovern strain of type I Pneumococcus was the infecting organism. The following quotation from the authors' discussion gives clearly the essential conclusions drawn from their work: "It seems reasonable to conclude, however, from the results of the present and previous studies that optimum therapeutic responses in fulminating human infections with such organisms as the Pneumococcus and Streptococcus can be achieved by administration of sodium penicillin G no more frequently than every eight hours, and probably somewhat less frequently because of the slower elimination of penicillin in the human patient. Much less frequent dosage may be required for optimum effects when one is dealing with more or less circumscribed infections. It also is reasonable to conclude that the continued presence of inhibitory concentrations of penicillin G in plasma is not essential to a maximum therapeutic response. These conclusions would eliminate the alleged basis for the general clinical use of repository preparations of the penicillins as well as for the 3- to 4-hourly and intravenous treatment schedules."

PILCHER, Cleveland.

THE EFFECT OF PENICILLIN UPON THE CLOTTING ACTIVITY OF BLOOD IN NORMAL HUMAN SUBJECTS. RALPH E. DOLKART, BERNARD HALPERN, MARY LARKIN, FREDERICK L. DEY, and G. DE TAKATS, J. Pharmacol. & Exper. Therap. **96**:291 (July) 1949.

The clotting activity of blood in 24 normal subjects was measured before and after administration of 300,000 units of crystalline penicillin G in wax and oil, and in 4 subjects with the same dose in saline. There was no effect on the clotting time in either series.

PILCHER, Cleveland.

A PHARMACOLOGICAL STUDY OF N-METHYL-N'-(4-CHLOROBENZAHYDRYL) PIPERAZINE DIHYDROCHLORIDE—A NEW ANTIHISTAMINIC. JULIO C. CASTILLO, EDWIN J. DE BEER, and STANISLAUS H. JAROS, J. Pharmacol. & Exper. Therap. **96**:388 (Aug.) 1949.

Many papers are being written on the development and pharmacologic action of antihistamine agents; the results here presented are quite promising of therapeutic value. The antihistamine reported, chlorcyclizine, showed a marked activity against histamine in tracheal and intestinal segments of the guinea pig; and when given orally in relatively small doses it prevented or reduced for over 23 hours the bronchoconstriction following exposure of guinea pigs to an atmosphere of nebulized histamine. The drug was relatively nontoxic to animals in doses found to be effective in humans. The effects in man—to be reported elsewhere—are given as very satisfactory.

PILCHER, Cleveland.

PAIN RELIEF WITH HYPNOTIC DOSES OF BARBITURATES AND A HYPOTHESIS. ARTHUR S. KEATS and HENRY K. BEECHER, J. Pharmacol. & Exper. Therap. **100**:1 (Sept.) 1950.

This excellent study was made on 178 postoperative patients. A very interesting point is made in the introduction, namely, that early in these observations it appeared probable that there is an effect of barbiturates on "pathological" pain which does not become apparent in studies of experimentally produced pain. The discussion of some 22½ pages clearly points out numerous facts that should be considered by anyone who has frequent occasion to use drugs for the relief of pain or who is studying the question. The following are mostly direct quotations from the authors:

"Some of the complexities in studying and treating pain in man can be resolved by an appreciation of the contribution of both the original stimulus and the modification of this stimulus in making up the total picture of pain. Lacking more specific information we have categorically labeled these modifying influences as psychic and assume a wide range in the degree to which the psychic factor can operate in any individual. Support for this assumption is found in the observation that neurotic individuals differ markedly from normal individuals in their reaction to a painful stimulus, whereas their levels of pain perception are almost identical.

"This approach to the pain experience makes it unreasonable to conclude that patients obtaining pain relief from placebos or saline do not have 'real pain.' . . . The perception of inflicted pain represents the recognition of a threshold physical stimulus, whereas existing pain is the stimulus plus its associated psychic modification. It may be convenient and wise to consider the physical stimulus only as 'pain' and the combination of physical and psychic modification as 'suffering.' In man we are concerned with 'suffering'; in animals we are probably concerned primarily with 'pain.' Obviously man is the animal of necessity for the study of pain."

It was found that hypnotic doses of pentobarbital sodium intravenously relieved what has been called postoperative pain in 50 per cent of patients, in contrast to 20 per cent with saline and 80 per cent with morphine.

PILCHER, Cleveland.

ADDICTION LIABILITIES OF MORPHINAN, 6-METHYLDIHYDROMORPHINE AND DIHYDROCODEINONE. H. F. FRASER and HARRIS ISBELL, J. Pharmacol. & Exper. Therap. **100**:128 (Oct.) 1950.

Although addiction to morphine and its derivatives can be seen very rarely in pediatric practice, the subject must have general interest to pediatricians. The studies were made on morphine addicts or on volunteer former addicts. Observations for development of morphine-like euphoria were carried out by trained attendants. It was found that the three drugs induced morphine-like euphoria in former morphine addicts, and that all possessed addiction liability and produced withdrawal symptoms. These symptoms were mild with the 6-methyldihydromorphine.

PILCHER, Cleveland.

THE RENAL CLEARANCE AND PLASMA PROTEIN BINDING OF AUREOMYCIN IN MAN. JONAS H. SIROTA and ABRAHAM SALTZMAN, J. Pharmacol. & Exper. Therap. **100**:210 (Oct.) 1950.

Other observers have noted that antibacterial activity remains in the blood considerably longer with aureomycin than when other antibiotics are given in comparable amounts, that aureomycin may be found in high concentration in the urine up to 16 hours after a single oral dose of 0.5 to 0.75 gm., and that it may still be detected in low concentrations up to 35 hours or longer. To explain this seemingly anomalous situation this study was made in human subjects. The explanation is given in the summary in part as follows:

"The renal excretion of aureomycin is solely a process of glomerular filtration of the free (filterable) component. The antibiotic is neither reabsorbed nor secreted by the tubule cells. Its final concentration in the urine merely reflects the tubular reabsorption of water. As the free (therapeutically active) component of the drug is dissipated by excretion and metabolism, more of it is liberated from the protein-aureomycin complex. It is these characteristics which explain the prolonged therapeutic blood levels and relatively high urine concentrations obtained following a given dose of the drug."

PILCHER, Cleveland.

HUMAN PAIN THRESHOLDS DETERMINED BY THE RADIANT HEAT TECHNIQUE AND THE EFFECT UPON THEM OF ACETYLSALICYLIC ACID, MORPHINE SULFATE AND SODIUM PHENOBARBITAL. ROBERT A. KUHN and R. B. BROMILEY, J. Pharmacol. & Exper. Therap. **101**:47 (Jan.) 1951.

The studies were made on medical students during their laboratory course in physiology; in one study sucrose was used as a control for the acetylsalicylic acid, and in the other study phenobarbital sodium was used as a control for morphine sulfate. The subjects had no knowledge of the drugs they received nor of the data obtained until the study was completed. The pain threshold determinations were made on a 1.5-in. (3.8-cm.) square of skin in the center of the forehead by a standard procedure with which the authors have had considerable experience. The drugs were given in standard doses: acetylsalicylic acid, 0.9 gm. in capsule, with an equal amount of sucrose in capsule as control; morphine, 0.016 gm. (0.25 grain), and phenobarbital sodium, 0.096 gm. (1.5 grains) subcutaneously. A comparison of thresholds either before and

after acetylsalicylic acid administration or sucrose and after acetylsalicylic acid administration reveals that the effect of acetylsalicylic acid upon the pain threshold as determined in these experiments is negligible.

All subjects noted systemic effects of the morphine and phenobarbital, such as dizziness or "light-headedness" with the former and dizziness or sleepiness with the latter.

The final conclusions of this study on 37 subjects were that acetylsalicylic acid and phenobarbital sodium were without effect on pain threshold, and that the effect of morphine sulfate (0.016 gm.) varied from person to person—slight, if any, in some persons, rather marked in others.

The authors state that in the morphine sulfate experiment, phenobarbital was used as a control drug rather than distilled water or isotonic sodium chloride solution in the hope that the subjects would not be able to distinguish the symptoms caused by the barbiturate from those due to the opium derivative. This expectation was, to their surprise, realized in all subjects. The failure to experience any euphoria, which is commonly believed to be one of the major effects of morphine administration, probably accounts for the inability of the subjects to recognize the nature of the drug injected.

PILCHER, Cleveland.

TREATMENT OF FLUOROACETATE POISONING IN MICE AND DOGS. W. W. TOURTELLOTTE and J. M. COON, J. Pharmacol. & Exper. Therap. **101**:82 (Jan.) 1951.

The use of fluoroacetate as a rodenticide is well known, as is its toxicity to other animals and to man, in the latter group children being the ones most liable to poisoning. In mice either sodium acetate or ethanol raised the fatal dose of fluoroacetate three to four times, but the combination of the two raised the dose to 12 times when it was given fairly promptly after the poison had been taken.

The antidotal effect was practically negative in dogs unless the antidote was given immediately after the fluoroacetate, or as an adjunct to phenobarbital given within 30 minutes of the poisoning. By the use of phenobarbital therapy and by starting treatment half an hour to three hours after poisoning, 100% of dogs poisoned orally with approximately twice the fatal dose of fluoroacetate were saved; with four times the fatal dose there was only 17% survival; no dogs survived six times the fatal dose when barbiturate was given half an hour after the fluoroacetate.

PILCHER, Cleveland.

SALICYLAMIDE: PHARMACOLOGY, FATE AND CLINICAL USE. MANUEL LITTER, ANIBAL RUIZ MORENO, and LEON DONIN, J. Pharmacol. & Exper. Therap. **101**:119 (Feb.) 1951.

From work on animals by these authors and from reports of studies in the literature, the authors thought that salicylamide was well worth a trial in man in rheumatic fever and other arthritides (rheumatoid arthritis, osteoarthritis, fibrositis). A total of 118 patients were studied, of whom but seven had rheumatic fever. The dose was 2.0 gm. given every four to eight hours repeatedly.

Repeated administration of the drug in the doses administered has not led to any evidences of its accumulation or any harmful effects thereof. Salicylamide appears to be useful in rheumatoid conditions and is better tolerated than salicylates. However, as in all instances of newly introduced drugs in the treatment of disease, more study will be required before it can assume its final place in the therapeutic armamentarium. Significantly beneficial results were obtained in a relatively high percentage of the total number of patients in the series. In the series of patients with acute rheumatic fever, the number is quite small, but the results appear to be distinctly promising.

PILCHER, Cleveland.

THE ADSORPTION OF DIGESTIVE ENZYMES BY SULFONAMIDES. GEORG CRONHEIM and J. STANTON KING JR., J. Pharmacol. & Exper. Therap. **101**:230 (Feb.) 1951.

The experiments reported were laboratory studies using all the sulfonamides that have been used clinically (eight) and others not used in therapeutics. The enzymes were pepsin and trypsin in crude and crystalline form, pancreatin U. S. P., and a commercial type of malt diastase. The

results which are reported in this paper indicate that all enzymes tested are adsorbed by sulfonamide particles. However, quantitative differences exist between various sulfonamides, and in the case of pepsin, also between the pure and impure preparation. It has also been found that adsorption destroys part of the pepsin, as indicated by its activity after desorption from the sulfonamide.

The authors suggest that the adsorption of the enzymes on the sulfonamides could affect the digestive processes. Studies on this point would be very interesting, but whether it would be sufficient to lessen the effect of the drugs in disease would probably be difficult to determine.

PILCHER, Cleveland.

CLINICAL STUDIES ON THE ACTIVITY OF ORALLY ADMINISTERED CORTISONE. GEORGE W. THORN, ALBERT E. RENOLD, D. LAURENCE WILSON, THOMAS F. FRAWLEY, DALTON JENKINS, JOSE GARCIA-REYES and PETER H. FORSHAM, New England J. Med. **245**:549 (Oct. 11) 1951.

The authors studied the effects of oral cortisone therapy on certain adult diseases and on specific physiologic response mechanisms common to both adults and children.

The clinical efficiency of the oral preparation given at six-hour intervals was proved and was seen to be about equal to that of the intramuscular preparation given once a day. The total required daily dosage of the steroid given orally and intramuscularly was approximately the same. The action of cortisone is more rapid when it is given orally and the levels obtained are higher, but the effects obtained are not as prolonged as in the intramuscular form. All of the metabolic actions of intramuscular cortisone may be produced by the oral form and hence the same precautions must be observed with either method.

These facts are of interest to pediatricians in view of the opportunity to avoid intramuscular injections in young patients and still obtain full therapeutic response.

WHEELOCK, Denver.

STUDIES ON THE ADMINISTRATION, ABSORPTION, DISTRIBUTION AND EXCRETION OF AUREOMYCIN IN CHILDREN WITH OBSERVATIONS CONCERNING TOLERANCE, DOSAGE SCHEDULES AND CERTAIN THERAPEUTIC INDICATIONS. COLEMAN M. WHITLOCK JR., ANDREW D. HUNT JR., and SYLVIA G. TASHMAN, Pediatrics **6**:827 (Dec.) 1950.

Data are presented on the administration, absorption, distribution, and excretion of aureomycin in children. From these data, tentative oral and intravenous dosage schedules of, respectively, 11 mg. per kilogram of body weight every four hours and 6.6 mg. per kilogram of body weight every 12 hours are proposed. The same total daily oral dose (60 mg. per kilogram of body weight) divided into less frequent separate doses than every four hours might prove equally effective and well tolerated. The possibility of uptake of aureomycin by some or all of the cells of the human body is also suggested. The observation of apparent photosensitivity occurring during aureomycin ingestion is reported.

FROM THE AUTHORS' SUMMARY.

A HOME PLAY AND OCCUPATIONAL PROGRAM FOR THE BEDFAST CHILD: THE COUNTERPANE COURSE. FRANCIS F. SCHWENTKER, ANNE FELTS EPPERSON, and ARCHIBALD HART, Pediatrics **7**:44 (Jan.) 1951.

Many children ill at home or in hospitals are denied the advantage of a planned recreational program. A course has been devised which is complete with adequate instruction books and materials suitable for children 7 to 12 years of age.

FROM THE AUTHORS' SUMMARY.

ELECTRIC BUNTING TO MAINTAIN BODY TEMPERATURE DURING EXCHANGE TRANSFUSION. P. VOGEL, R. E. ROSENFIELD, and M. STEINBERG, Pediatrics **7**:207 (Feb.) 1951.

A washable electric blanket bunting has been designed to maintain the body temperature of an infant throughout an exchange transfusion and also in the post-transfusion period if a heated crib is not available. The bunting may be used for all routes of the administration. The blanket

has been constructed by the General Electric Company, is made of washable materials, and operates in principle as the commercial electric blanket (110 volts, 60 cycles A.C.). It can be regulated to any desired temperature, with a maximum of 42 C., which prevents burns.

FROM THE AUTHORS' SUMMARY.

STUDIES ON THE ABSORPTION AND DISTRIBUTION OF CHLORAMPHENICOL. RICHARD S. KELLY, ANDREW D. HUNT, JR., and SYLVIA G. TASHMAN, Pediatrics **8**:362 (Sept.) 1951.

Chloramphenicol is readily absorbed from the gastrointestinal tract. Peak serum levels, although usually reached within two hours, are occasionally not attained for six or more hours. In general, absorption is markedly more rapid than in the case of aureomycin, which seems to be absorbed slowly over a period of several hours.

Eleven milligrams per kilogram of body weight, an adequate single dose of aureomycin, in the case of chloramphenicol produces serum levels too low to be detected by the authors' method. Twenty-two milligrams per kilogram produces two-hour levels averaging 8.3 γ per cubic centimeter, and 44 mg. per kilogram raises this level to a mean of 22 γ per cubic centimeter.

Rectal administration of perforated chloramphenicol capsules produces peak serum levels approximately one-fifth of those effected with comparable oral dosage.

Diffusion of chloramphenicol into cerebrospinal fluid occurs readily. After a few days' administration spinal fluid levels, in three cases, were approximately 50% of the serum levels.

These data suggest that effective oral dosage of chloramphenicol ranges from 22 to 44 mg. per kilogram to the dose, and that the antibiotic should be given at 6- to 8-hour intervals.

FROM THE AUTHORS' SUMMARY.

LABORATORY ASPECTS OF ANTIBIOTIC THERAPY. EARLE H. SPAULDING, Pediatrics **8**:406 (Sept.) 1951.

For a year or two after the introduction of penicillin many clinicians believed that culture studies were no longer needed; as a result the number of specimens submitted to the laboratory declined sharply. But the appearance of streptomycin reversed this trend, and the subsequent discoveries of chloramphenicol, aureomycin, and terramycin have created a need for culture study which greatly exceeds the level existing before the days of penicillin.

Prior to the advent of antibiotics the primary function of the infectious disease laboratory was to isolate and identify the causative organism. At the present time, however, the principal contribution of the laboratory is the determination of in vitro susceptibility to antibiotics.

Bacterial strains within a single species exhibit highly specific susceptibility patterns when tested with the several antibiotics currently available. Because in vitro susceptibility tests constitute the only certain method for predicting clinical response, the bacteriology laboratory is playing an expanding part in the choice and control of antibiotic therapy. Although there is no need for bacteriologic studies in the vast majority of infections, such studies are sometimes essential to the successful management of severe acute, refractory, and relapsing infections. The correlation between laboratory and clinical results is very good, provided allowances are made for certain factors discussed in this paper. Antibiotic susceptibility tests are entirely practical and should be used routinely in all laboratories which do bacterial cultures.

FROM THE AUTHOR'S SUMMARY.

EARLY INTEREST IN PEDIATRICS IN SOUTH CAROLINA. JOSEPH IOOR WARING, Pediatrics **8**:413 (Sept.) 1951.

Before the nineteenth century there were comparatively few writings on pediatrics in the United States. Waring mentions some of the better known writers, and offers by inference and quotation the thought that some of the earlier physicians in Charleston, such as Killpatrick, Dale, Chalmers, Ramsay, and Logan, represented a concentration of pediatric interest greater than in other parts of the country.

FROM THE AUTHOR'S SUMMARY.

METHOD OF OBTAINING ANAEROBIC ARTERIAL BLOOD SAMPLES FROM INFANTS. FRANK E. HYTTEN and RUTH B. CHERRY, Pediatrics **8**:518 (Oct.) 1951.

In order to obtain repeated, anaerobic, arterial blood samples from newborn infants safely, rapidly, and with minimum pain, so that crying can be avoided, a method has been developed for sampling cutaneous blood. By means of a special glass tube applied directly over a cruciform incision made in the soft tissue area containing the plexus of arterioles from the lateral malleolar artery, blood is transferred directly from the warmed foot to the pipettes used in the analysis of oxygen and carbon dioxide.

FROM THE AUTHORS' SUMMARY.

THE SOUTH'S SERVICE TO THE CRIPPLED CHILD. WILLIAM L. FUNKHOUSER, South. M. J. **44**:124 (Feb.) 1951.

The author lists eight conditions in addition to orthopedic conditions which handicap children and which should be included in programs to aid crippled children. He shows that these needs are now met inadequately by the 16 Southern states and the District of Columbia. Recommendations for improvement in the care of crippled children are included. One of the greastest needs is more funds.

LOGAN, Rochester, Minn.

PHAEOCHROMOCYTOMATA IN CHILDREN. DOUGLAS HUBBLE, Arch. Dis. Childhood **26**:340 (Aug.) 1951.

A case is described of multiple pheochromocytomata (four tumors) occurring in a boy aged 11. A characteristic paroxysmal phase lasted from the age of 6½ to 8 years. For a further three years the boy was in good health, except for symptoms of sweating, restlessness, nocturnal enuresis, and occasional fatigue. This was the phase of sustained hypertension. The third phase of hypertensive heart failure was imminent when he died after a diagnostic laparotomy. The clinical signs and electrocardiographic evidences of changes of advanced hypertensive disease were confirmed by the state of the arteries and arterioles at necropsy.

References are given to other examples in the literature of pheochromocytomata in children diagnosed during life.

Massive retinal exudate was coincident with the hypertensive phase. The amount of exudate was much greater than has been described as accompanying either pheochromocytoma or essential hypertension. The exudate regressed during the phase of sustained hypertension. The retinal changes were associated with a pleocytosis in the cerebrospinal fluid. Expert ophthalmological opinion is not agreed as to whether the changes in the fundi were related to paroxysmal hypertension. The response of the blood pressure to the benzodioxan (piperoxan hydrochloride) test was positive for this boy, but the injection of perirenal air was not completely successful. Diagnosis of these tumors is easier in children than it is in adults, if the repeated use of the sphygmomanometer is not forgotten. The excretion of gonadotropins and 17-ketosteroids was low in this boy, and the significance of this fact is discussed. The pharmacological nature of the tumors is described.

KELLY, Milwaukee.

EFFECTS OF FAULTY POSTURE. H. A. BURT, Proc. Roy. Soc. Med. **43**:187 (March) 1950.

Opinion of what constitutes good posture has undergone many changes in the course of time. Wide variation in definition of normal posture is necessary owing to variation in physique. The plumb line and inclinometer are used as a basis for measurement. Types of faulty posture and the physical findings and sequelae associated therewith are described. Treatment must be carefully worked out and painstakingly carried out to obtain improvement which is directed to improve agility and mobility, muscle relaxation, strengthening of weak groups, and reeducation of postural reflex.

HEARD, Monterey, Calif.

PHYSICAL METHODS FOR CONTROLLING HYPERPYREXIA IN CHILDREN. N. G. MOJUMDAR and B. BHATTACHARYA, Ind. J. Pediat. **18**:10 (Jan.) 1951.

The authors advocate ice water enemas to reduce fever in cases of hyperpyrexia.

McGUIGAN, Evanston, Ill.

FACTS ABOUT ALCOHOLIC INTOXICATION IN CHILDREN. L. CAUSSADE, N. NEIMANN, and H. BLANC, Pédiatrie **38**:531 (No. 6) 1949.

The authors point out that in acute cases of alcoholic intoxication coma is the presenting symptom and that in chronic cases cirrhosis may occur at a very early stage. In one case acute intoxication with coma occurred as a result of erroneous injection of 20 cc. of 95% alcohol subcutaneously. The cases of two patients with chronic intoxication with cirrhosis are described; one patient received alcohol as a tonic, and the other inhaled alcohol by spending several hours, almost daily, in a distillation room where the air was laden with alcohol vapors.

GLASER, Jerusalem, Israel.

CASE OF PETROL POISONING. JAQUELINE BACH and J. CAEN, Ann. pædiat. **177**:20 (July) 1951.

The authors report a case of petrol poisoning which was followed by pneumonia. The pneumonia proved to be resistant against the usual antibiotics, and relapse occurred on the 18th day. The pathogenesis of the lung process is discussed, and other cases from the literature are mentioned.

FROM THE AUTHORS' SUMMARY.

ISOHEMAGGLUTININS IN MAMMARY SECRETION AND IN BLOOD SERUM IN THE FIRST DAYS OF THE PUERPERIUM. BIANCA RONDININI, Clin. pediat. **33**:95 (Feb.) 1951.

The titers of the antibodies of the A-B-O system were determined in the blood sera and in the mammary secretions of mothers on the first and the sixth days of post partum. The blood titer on the first day was lower than that of the colostrum, suggesting selective secretion. On the sixth day, the blood titer had shown a slight rise but the titer in the breast milk was markedly lower than it had been in the colostrum. It would appear that the condition of a newborn child with hemorrhagic disease may be damaged by the ingestion of colostrum with its high antibody titer.

HIGGINS, Boston.

THE THERAPEUTIC VALUE OF A NEW SULFONAMIDE PREPARATION (FORMOCIBAZOL). R. DE BLASI and TANGHERONI, Minerva pediat. **2**:434, (Sept.) 1950.

"Formocibazol" is a condensation product of sulfathiazole and formaldehyde. This product proved efficacious in the treatment of dysentery, typhoid, and paratyphoid in children. The drug almost completely eliminated the bacilli of the coli group from the stools. This observation points to the possible use of the drug in prophylaxis in typhoid infections.

HIGGINS, Boston.

HYDROTHERAPY FOR CHILDREN WITH A BRINE CONTAINING BROMIDE AND IODIDE. L. LANDUCCI, Pediatria **58**:705 (Sept.) 1950.

Repeated hydrotherapeutic treatments were given to 207 children at the Children's Bathhouse at Salsomaggiore to determine the effects of salt water containing bromides and iodides on the various physiological and biochemical body functions. The findings indicated a stimulus of the general cellular metabolism, with improvement in general well-being, a better appetite, a gain in weight, and a subsequent reduction in respiratory infections. Clinical benefit was observed in children with enlarged tonsils and adenoids and in children with asthma and with rheumatic fever.

HIGGINS, Boston.

LEVELS OF CHLORAMPHENICOL IN THE BLOOD, URINE, AND CEREBROSPINAL FLUID AFTER ORAL AND RECTAL ADMINISTRATION. PIERO MOGGI, Riv. clin. pediat. **49**:115 (Feb.) 1951.

The author determined by titration with use of the turbidimetric method the levels of chloramphenicol in spinal fluid, urine, and blood of children aged 6 to 24 months after one or several oral or rectal administrations.

For children 10 to 12 mg. per kilogram per dose is sufficient; administration every five hours is useful, in spite of the rapid fall of hematic rate. Rectal administration is as effective as oral and must be preferred in cases of intolerance.

FROM THE AUTHOR'S SUMMARY.

COMMENTS ON THE TREATMENT OF TOXIC STATES WITH HUMAN PLASMA. ENRIQUE DE YTURRIAGA and SOFIA GONZALEZ BOTILLA, Acta pediat. españ. **82**:1187 (Oct.) 1949.

The authors, two pediatricians from the Spanish Institute of Hematology and Hemotherapy, Health Department of Madrid, base their conclusions on six years' experience with this department, and disagree with Franconi's treatment. Franconi's outline of treatment leaves the use of plasma at the end of the devices to be used to combat toxic states in infants suffering from diarrhea, dysentery, acidosis or alkalosis, or hypoproteinemia from whatever cause. The authors give a review of the various theories for the cause of these conditions and agree that none of the theories can be made to cover all cases, but they state that the cause of death is circulatory collapse following any of the conditions mentioned above, that is, dehydration acidosis, severe infections, etc. They also give an excellent chart, listing the toxic symptoms in the sick child and the pathology responsible for each particular symptom.

Ramos and Oppenhermu say, "To resist the use of plasma, or to use it in small doses in dehydration and similar toxic states with the thought that many will recover without it, is just as reprehensible as to withhold sulfonamides from cases of pneumonia because they will recover without it." The authors of this report say that plasma will combat shock, increase blood volume, combat dehydration, and add natural protein, all at the same time. Plasma should be administered whenever humanly possible. Later, salt and water can be restored, medication can be given to stimulate the kidneys, and adequate calories and vitamins can be prescribed. In other words empirical use of plasma is advised. Even specific therapeutics such as antibiotics and sulfonamides should be secondary to plasma. In their experience a child can begin to eat much sooner with plasma treatment than with the slower and more conservative treatment schedules.

ALLEN, Santa Fe, N. M.

IMPORTANCE OF BIOSTATISTICS IN PEDIATRICS. FRANCISCO J. MENCHACA, Bol. inst. internac. am. protec. infancia **25**:203 (Sept.) 1951.

Biostatistics must be considered as an element of extraordinary value and efficacy in the medicosocial action of pediatrics, as much of value in the private or official practice of the pediatrician as in the work of scientific research. Likewise, biostatistics has a significant part in community studies or surveys, which, together with the problems of sanitary administration, must interest pediatricians who want to win the fight against infant mortality. The incorporation of biostatistics into the pediatric field can be stimulated by including subjects related to it in programs of congresses and conferences; by establishing specialized committees or sections in professional associations; by favoring studies, works, and publications on the subject; by granting prizes or other recompenses to statistical researches in infancy; by organizing brief postgraduate courses, and by making contacts and interrelations between pediatric societies and statistical bureaus. It is also well to include methodological statistics in the course of study in medical schools.

FROM THE AUTHOR'S SUMMARY.

INTRAPERITONEAL BLOOD TRANSFUSION IN INFANTS. F. J. NIESERT, Deutsche med. Wchnschr. **75**:619 (May 5) 1950.

Directions are given with regard to the technique, the dosage, and, if desirable, the time for repetition of the intraperitoneal blood transfusion. This method of transfusion is regarded as the method of choice for the newborn and infancy periods.

AMBERG, Rochester, Minn.

FEER'S NEUROSIS: A HYPERSENSITIVITY REACTION OF THE CHILD TO MERCURY MEDICATION. MARIANNE KLEIN, Med. Klin. **46**:101 (Jan. 26) 1951.

Within four months seven children between 1 and nearly 8 years of age were observed; all had been treated with santonin and mild mercurous chloride for worms. In three cases the urine contained 4 to 70 γ of mercury; the other patients were not examined. In several cases the blood pressure was not elevated, and the diagnosis of erythredema polyneuropathy ("Feer's neurosis") might perhaps have been better founded.

AMBERG, Rochester, Minn.

ANTIHISTAMIN INTOXICATION IN A CHILD. HILDEGARD BOCK, Med. Klin. **46**:1012 (Sept. 21) 1951.

A 14-month-old girl took tablets of an antihistaminic drug, tripelennamine (pyribenzamine®) hydrochloride, probably five to eight times the usual dose per day for its age. At some time afterwards the child was admitted to the hospital with vomiting and slight spasms. She was apathetic but conscious. There was disorder of the equilibrium, some lack of coordination of the upper extremities, and strabismus. A tachycardia was present. The child recovered.

AMBERG, Rochester, Minn.

USE OF PENICILLIN SUPPOSITORIES. M. GAIDA and G. NEUMEYER, Med. Klin. **46**:1110 (Oct. 19) 1951.

Directions are given for the preparation of penicillin suppositories. The dosage for children was 125,000 to 250,000 units, usually 125,000 units two or three times daily. One to four suppositories were given daily. The results were good.

AMBERG, Rochester, Minn.

EFFECT AND DOSAGE OF MAGNESIUM SULFATE IN CHILDREN. HEINZ AUE, Monatsschr. Kinderh. **97**:83 (June) 1949.

It was found that a 15% solution of magnesium sulfate was an effective and rapidly acting cathartic in children. The opportunity to test various solutions arose when children with ascariasis were being treated with chenopodium oil. This concentration was better tolerated as regards nausea and emesis than stronger (hypertonic) solutions. Isotonic solutions, as recommended by many authors, were found to be too slow acting and often to be without cathartic effects. The recommended doses ranged from 100 to 125 cc. for 2 to 3 years of age to 375 cc. for 12 years of age.

HARTENSTEIN, Chicago.

STREPTOMYCIN IN PEDIATRICS. OTTO RUZIOZKA, Wien. klin. Wchnschr. **62**:225 (March 31) 1950.

At the University of Vienna Children's Hospital 88 patients with tuberculous meningitis were treated with streptomycin. Of these, 43 died. Twenty-two patients were dismissed as cured. The longest period of cure at the time of writing was 18 months. Miliary tuberculosis of the lungs was treated in 18 cases; in 16 of these the response was good. A few other forms of tuberculosis were treated. Little detail is given.

AMBERG, Rochester, Minn.

ALLERGIC ANTIBODIES AFTER PENICILLIN THERAPY. M. FROBENIUS and JUTTA MARTIN, Ztschr. Kinderh. **66**:346, 1949.

In eight of nine cases the presence of antibodies against penicillin was demonstrated by the passive transfer method with serum from infants under 1 year of age who received penicillin therapy. The significance of these experiments is pointed out, not only with regard to penicillin therapy but also because they demonstrate the ability of infants to produce antibodies.

GLASER, Jerusalem, Israel.

UNUSUAL CAUSES OF SUFFOCATION IN CHILDREN. JOSEF VANEK, Pediat. listy **5**:282, 1950.

In three infants, aged 38 days, 2 months, and 4 months respectively, severe stridor was observed; in two it had started immediately after birth, in the third at the age of 5 weeks. The first and the third patients died of suffocation, whereas acute gastroenteritis was at least a concomitant cause of death for the second. In none was the cause of the stridor established before the postmortem examination. In the first there was a serous cyst about 1 cm. in diameter at the root of the tongue; in the second the finding was similar, the cyst measuring 13 mm. In the third a very unusual condition was found, which, on microscopic examination, turned out to be a hemangioma. The hemangioma was situated along the outer wall of the trachea on the left; it penetrated the wall of the larynx and of the trachea in two places, causing a swelling beneath the mucosa. Although the stenosis as seen at the postmortem examination was not very marked, one may imagine that during life the tumor when filled with blood was sufficient to cause stridor and suffocation.

FROM THE AUTHOR'S SUMMARY.

ACUTE QUINIDINE POISONING IN A 3 YEAR OLD CHILD: WITH SPECIAL REFERENCE TO THE ELECTROCARDIOGRAPHIC CHANGES. L. E. WARFVINGE, Acta pædiat. **39**:262 (No. 3) 1950.

A study was made of the electrocardiographic changes presented by a 3-year-old boy who had received at least 1.6 gm. of quinidine sulfate. The characteristic prolongation of P waves and QRS interval and impairment of auriculoventricular and intraventricular conduction were found. A control study after 18 hours demonstrated a normal electrocardiogram.

FROM THE AUTHOR'S SUMMARY.

LEAD POISONING OF CHILDREN IN A TYPOGRAPHER'S FAMILY. INGEMAR BJÖRKHAGEN, Svenska läk.-tidning. **45**:2269 (Nov. 19) 1948.

A report is given of a family with three children, the father of which, a typographer, had brought home out-mustered leaden types to his children to play with. Two months later two of the children, ages 8 and 4 years, displayed colic and intestinal troubles but no other clinically or roentgenologically demonstrable signs of lead poisoning, except an increased lead content of the urine in the first child, who also suffered from purpura. The younger child was not examined until six months after exposure. These two children were thumb suckers, while their 7-year-old brother, who was not a thumb sucker, had only played with the types and had remained healthy.

WALLGREN, Stockholm, Sweden.

NERVUS VESTIBULARIS CONTROL DURING TREATMENT WITH STREPTOMYCIN. B. BARR, L. E. FLOBERG, C. A. HAMBERGER, and H. J. KOCK, Svenska läk.-tidning. **45**:2456 (Dec. 17) 1948.

With a daily dose of 0.5 to 1 gm. and a total dose of 60 gm. of streptomycin, the risk of lesion of the vestibular nerve is relatively small. It is necessary to control renal function because a normal excretion is a prerequisite for administration of ordinary doses of streptomycin. Vestibular nerve disturbance is easily compensated in children, seldom fully compensated in adults.

WALLGREN, Stockholm, Sweden.

ELECTRICAL BURNS OF THE MOUTH. J. C. TUMMERS, Maandschr. kindergeneesk. **17**:249, 1949.

Tummers describes 10 cases of electrical burns of the mouth which were caused by the children putting into their mouths the switch of an electric flatiron or vacuum cleaner which was in contact with electric current. The usual signs were necrosis of the tongue, lips, and gums, with marked swelling, a bacon-like precipitate, excessive discharge of saliva, and halitosis. Sometimes tube feeding through the nose was necessary. The cosmetic effects after the healing of the necrosis were not too bad; in only a few cases were surgical corrections required. The necrotic tissue showed the changes characteristic of burns caused by a high-voltage current.

VAN CREVELD, Amsterdam, Netherlands.

KEROSENE POISONING. S. KAFILUDDI, Maandschr. kindergeneesk. **18**:442, 1950-1951.

Nine cases of kerosene poisoning in children are reported. One case was due to ingestion of "shelltox," a solution of benzyl benzoate-chloramphenothane-ethyl amino-benzoate (DDT) in petroleum. A summary is given of the symptoms observed in these cases and of those reported in the literature on this subject. Attention is especially drawn to the causes and nature of the respiratory complications.

FROM THE AUTHOR'S SUMMARY.

KINETIC AND OSMOTIC POINTS OF VIEW LEADING TO THE DETERMINATION OF MOLECULAR WEIGHTS OF PROTEIN AND OTHER SUBSTANCES. HECTOR A. DIEU, Maandschr. kindergeneesk. **19**:293 (Oct.) 1951.

Dieu discusses from the kinetic and osmotic points of view a ratio leading to the determination of molecular weights of proteins and other substances which can be spread in monolayers. He then applies such a ratio to the molecular weight estimation of some substances, such as papain, laurylpyridinium chloride, and cellulose diacetate, either by Bull's method or by Guastalla's method. He also emphasizes some theoretical or practical difficulties arising from the methods.

FROM THE AUTHOR'S SUMMARY.

News and Comment

PERSONAL

Sinai Announces Appointment of Dr. Gordon.—Sinai Hospital, Baltimore, announces the appointment of Dr. Harry Gordon as full-time Chief of Staff in Pediatrics, effective as of Jan. 1, 1952. Concurrently, in accordance with a recent agreement between Sinai Hospital and the Johns Hopkins medical institutions, Dr. Gordon was appointed Associate Professor in Pediatrics at The Johns Hopkins University School of Medicine and Pediatrician on the staff of Johns Hopkins Hospital. Dr. Gordon resigned from his position as Professor of Pediatrics at the University of Colorado School of Medicine and as Pediatrician-in-Chief at Colorado General Hospital and Denver General Hospital to accept the appointment at Sinai Hospital.

ANNOUNCEMENTS

New Child Care Unit.—On Feb. 18, 1952, the Michael Reese Hospital, Chicago, opened a Child Care Unit in the Institute for Psychosomatic and Psychiatric Research and Training. This unit is intended for the care of all phases of psychiatric and psychosomatic problems in children. Children, approximately between the ages of 6 and 12 years, will be accepted for observation, diagnosis, and evaluation, and for short- or long-term therapy. The children will be offered the benefit of psychiatric, pediatric, psychological, electroencephalographic, and other laboratory facilities for diagnosis. Specially trained personnel in the nursing, occupational therapy, and teaching specialties are available as auxiliary therapists.

Beds are available for the private patients of recognized psychiatrists who will be in complete charge of their patients. These psychiatrists will have use of play-therapy rooms and the full cooperation of the resident and full-time auxiliary staff of the unit. Psychosomatic patients must be under the joint care of a pediatrician and a child psychiatrist.

Three-Day Course for Pediatricians, General Practitioners, and Health Officers.—The Pediatric Department of the Memorial Center for Cancer and Allied Diseases announces a comprehensive three-day course on May 21, 22, and 23, 1952, for pediatricians, general practitioners, and health officers. Current developments and established methods in diagnosis, differential diagnosis, and management of benign and malignant tumors, Hodgkin's disease, leukemia and reticuloendothelioses in childhood are included. Contents of the course are as follows: demonstrations; examinations of children in pediatric, surgical, chemotherapy, and radiotherapy clinics; ward rounds and seminars under the direction of the staffs of Memorial Hospital and Sloan-Kettering Institute for Cancer Research. The fee is $35.00. For further information address the Director of Pediatric Service, Memorial Center, 444 E. 68 St., New York.

Books

Communicable Diseases. Edited by Roscoe L. Pullen. Price, $20.00. Pp. 1035, with 235 figures, 35 illustrations on 20 color plates. Lea & Febiger, Philadelphia, 1950.

As the field of medicine has become more and more complex, authors of complete texts have not attempted to cover an entire field unaided. The modern trend has been to gather together a group of writers to cover the specific subjects in a field, but this has not been done heretofore in the field of communicable disease. Now, Dr. Pullen has done this, and as editor he has produced a larger and more complete text than any we have seen. The contributors are largely from the staff of the Charity Hospital of Louisiana and from the United States Public Health Service. The names of many will not be well known to most readers.

The subjects are grouped according to general manifestations rather than according to etiologic agents. Thus diseases with predominantly skin manifestations are grouped together, and those with predominantly respiratory symptoms are grouped together. Numerous photographs are included, with particularly good ones of syphilitic lesions. However, it is disappointing that other color plates were made from poor paintings of skin lesions rather than from clinical photographs.

Most of the text is well written and apparently authoritative, especially the sections on syphilis, typhoid, and shigellosis (bacillary dysentery). However, certain chapters, such as that on Vincent's infections and that on encephalitis, reveal a surprising lack of knowledge. It is suggested that the authors wrote these sections some years ago and did not have an opportunity to bring them up to date.

It is a tremendous undertaking to produce a text covering a field that is changing as rapidly as this one. All in all the authors have done well and have provided a good reference book for both students and practitioners.

Pathology of the Fetus and the Newborn. By Edith L. Potter, M.D. Price, $19.00. Pp. 592, with 921 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1952.

Occasionally a person is privileged to have access to an unusual amount of material for study in a special field of medicine. Books that share with others the benefits of such an experience are, however, rare. Dr. Potter has written such a book.

Because of her interest in the fetus and newborn infants, Dr. Potter has for 18 years been accumulating material for this book. It is based on more than 6,000 autopsies performed at the Chicago Lying-in Hospital on infants and fetuses dying there, from other sources during that time, and from tissues examined at over 3,000 additional autopsies performed elsewhere by pathologists from the Chicago Department of Health. Also during those years she was able to review over 10,000 protocols of autopsies on live-born infants, who died under one year of age, from other hospitals in Chicago.

It is, however, not only from the vastness of this material that the value of her book stems but also from the objective and critical evaluation of it which she, as a scientist and a teacher, is able to give. Dr. Potter's long and intimate association with a large obstetrical hospital of a university medical school has given her a clinical and public-health approach as well. This is reflected in her book and enhances its value.

The development of the embryo and the fetus and the factors which influence this development are concisely treated. Neonatal adjustments and conditions which may adversely influence them are frequently emphasized throughout the text. It is in this that she reveals an appreciation of clinical problems which is not as common among pathologists as it might be.

Causes of fetal and infant death, methods of postmortem examination, and a thorough discussion of the pathologic findings in deaths from various causes come next in the book. Following this there is full discussion of malformations, tumors, and pathologic conditions in the various tissues, organs, and organ systems.

The book is profusely illustrated with excellent photographs.

This book is of tremendous importance. It indicates in a vivid way how necessary for the welfare of the infant is cooperation between obstetricians, pediatricians, and nurses; it emphasizes the necessity of better understanding of fetal and neonatal physiology, and it illustrates the value of careful postmortem examinations in determining the cause of death.

Any physician engaged in obstetrics, pediatrics, or pathology will benefit by having this book and referring to it often.

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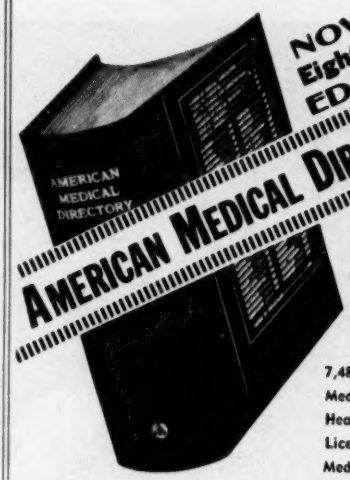

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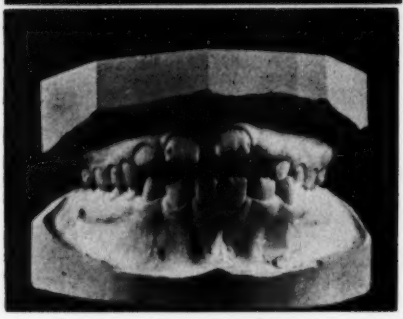

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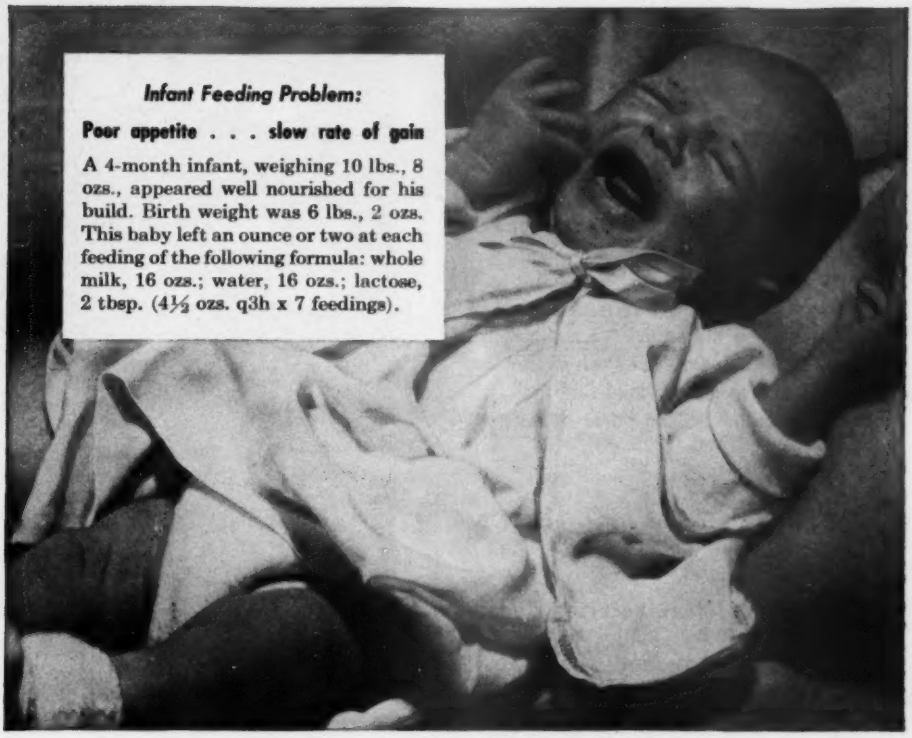

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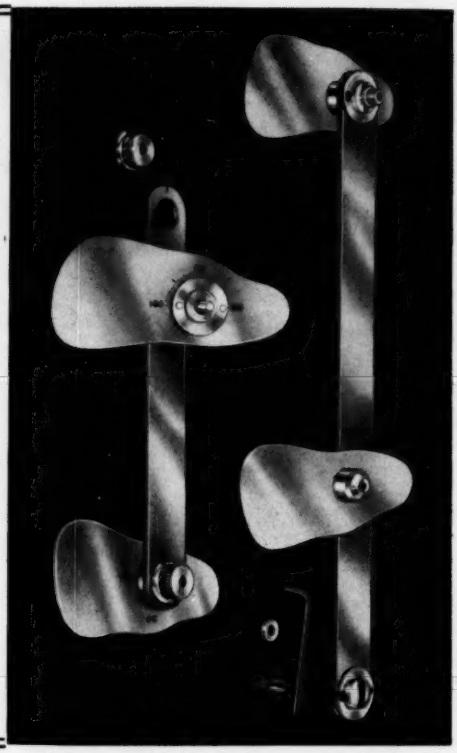

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*Jeans and Marriott, "Infant Nutrition"—4th Edition, Page 74.

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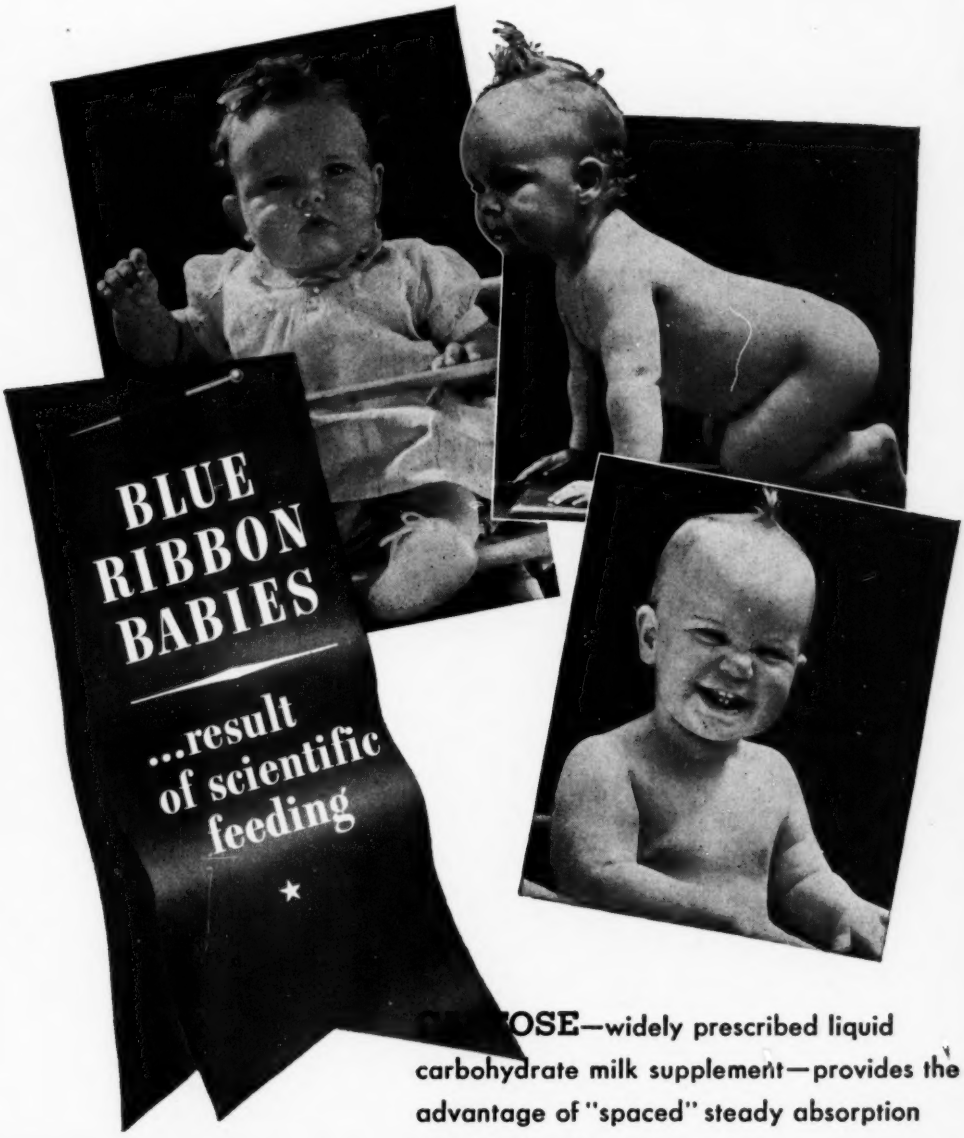

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